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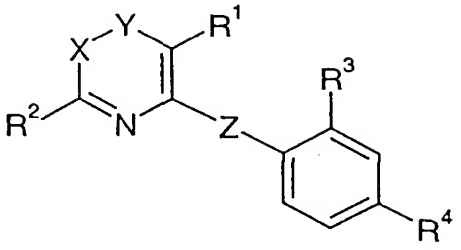
(54) Title: PYRIMIDINE, TRIAZINE AND PYRAZINE DERIVATIVES AS GLUTAMATE RECEPTORS

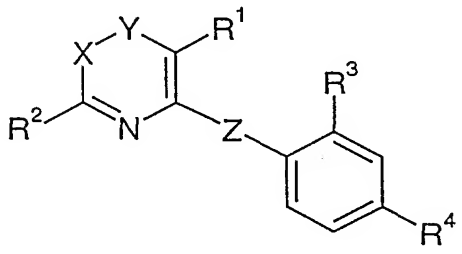


(I)

(57) Abstract: The present invention relates to pyrimidine, triazine and pyrazine derivatives of the general formula (I), wherein R^1, R^2, R^3, R^4, X, Y and Z have the significances given in the specification ,as well as their pharmaceutically acceptable salts. The invention further relates to medicaments containing these compounds, their preparation and to their use for the control or prevention of acute and/or chronic neurological disorders.

PYRIMIDINE, TRIAZINE AND PYRAZINE DERIVATIVES AS GLUTAMATE RECEPTORS

The present invention relates to pyrimidine, triazine and pyrazine derivatives of the general formula



I

wherein

R^1 signifies nitro or cyano;

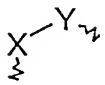
R^2 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $-(CH_2)_m\text{-}OR^{11}$, $-(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl, $-(CH_2)_m\text{-}NH\text{-}C(O)O\text{-}(C_1\text{-}C_7)$-alkyl, or $-(CH_2)_p$-pyridyl; and

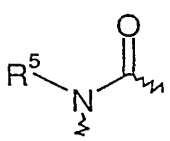
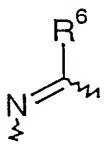
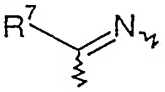
R^{11} signifies hydrogen or $(C_1\text{-}C_7)$-alkyl;

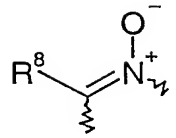
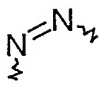
R^3 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, fluoro, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;



signifies

(a)  (b)  (c) 

(d)  or (e)  , wherein

R^5 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $(C_1\text{-}C_7)$-alkenyl, $\text{-}(CH_2)_m\text{-}OR^{11}$, fluoro-$(C_1\text{-}C_7)$-alkyl or $\text{–}(CH_2)_n\text{-}CN$;

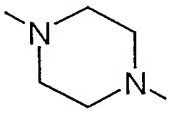
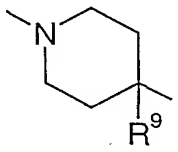
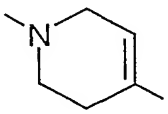
R^6 signifies $(C_1\text{-}C_7)$-alkyl, halogen, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, $\text{-O-}(CH_2)_m\text{-}OR^{11}$, -O-fluoro-$(C_1\text{-}C_7)$-alkyl or $\text{–}NHR^{12}$; and

R^{12} signifies $(C_1\text{-}C_7)$-alkyl, $\text{-}(CH_2)_m\text{-}OR^{11}$, $\text{-}(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl or $\text{-}(CH_2)_p$-pyridyl;

R^7 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or phenyl;

R^8 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or phenyl;

Z signifies

(i)  (ii)  (iii)  , wherein

R^9 signifies hydrogen, hydroxy or cyano;

m is independently from each other in each occurence 2, 3, 4, 5 or 6;

n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;

as well as their pharmaceutically acceptable salts.

It has now been found that the compounds of general formula I are antagonists at metabotropic glutamate receptors.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent

stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluRs are known and of these some even have sub-types. On the basis of structural parameters, the different second messenger signaling pathways and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

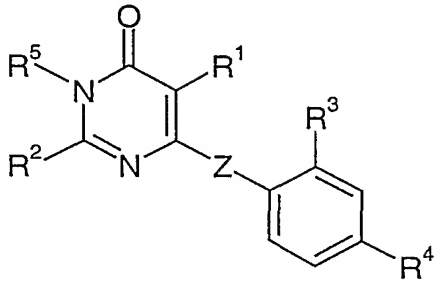
mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depression.

Objects of the present invention are compounds of formula I and pharmaceutically acceptable salts thereof and their use as pharmaceutically active substances. Methods for the preparation of the above mentioned substances and medicaments based on compounds in accordance with the invention and their production are also objects of the present invention as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

Preferred compounds of formula I within the scope of the present invention are those having the general formula



Ia

wherein

R^1 signifies nitro or cyano;

R^2 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $-(CH_2)_m\text{-}OR^{11}$, $-(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl, $-(CH_2)_m\text{-}NH\text{-}C(O)O\text{-}(C_1\text{-}C_7)$-alkyl or $-(CH_2)_p$-pyridyl; and

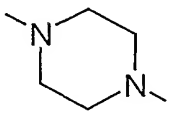
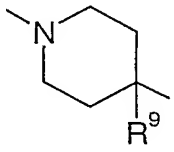
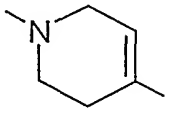
R^{11} signifies hydrogen or $(C_1\text{-}C_7)$-alkyl;

R^3 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, fluoro, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;

R^5 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $(C_1\text{-}C_7)$-alkenyl, $-(CH_2)_m\text{-}OR^{11}$, fluoro-$(C_1\text{-}C_7)$-alkyl or $-(CH_2)_n\text{-}CN$;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;

m is independently from each other in each occurence 2, 3, 4, 5 or 6;

n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;

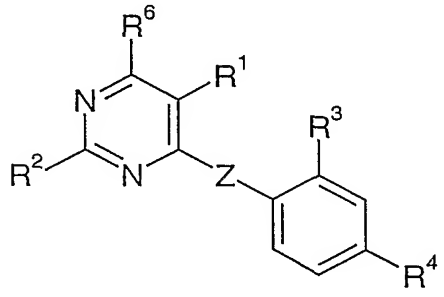
as well as their pharmaceutically acceptable salts.

Especially preferred are those compounds of formula Ia, wherein R^2 signifies $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; R^3 signifies hydrogen or fluoro and Z has the significances as defined above, wherein R^9 is hydrogen.

Even more preferred are compounds of formula Ia, wherein R^3 is hydrogen and R^5 signifies $(C_1\text{-}C_7)$-alkyl, $\text{-}(CH_2)_m\text{-}OR^{11}$ or fluoro-$(C_1\text{-}C_7)$-alkyl.

The following are examples of such compounds:
6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-3-(2-hydroxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-3-(2-methoxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one, and
3-ethyl-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one.

Also preferred are compounds of formula I within the scope of the present invention which have the general formula



Ib

wherein

R^1 signifies nitro or cyano;

R^2 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $\text{-}(CH_2)_m\text{-}OR^{11}$, $\text{-}(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl, $\text{-}(CH_2)_m\text{-}NH\text{-}C(O)O\text{-}(C_1\text{-}C_7)$-alkyl or $\text{-}(CH_2)_p$-pyridyl; and

R^{11} signifies hydrogen or $(C_1\text{-}C_7)$-alkyl;

R^3 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, fluoro, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, cyano or nitro;

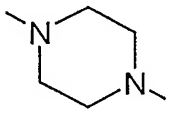
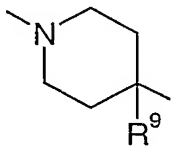
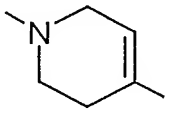
R^4 signifies hydrogen or fluoro;

R^6 signifies $(C_1\text{-}C_7)$-alkyl, halogen, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio,

$-O-(CH_2)_m-OR^{11}$, $-O$-fluoro-(C_1-C_7)-alkyl or $-NHR^{12}$; and

R^{12} signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl or $-(CH_2)_p$-pyridyl;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;

m is independently from each other in each occurence 2, 3, 4, 5 or 6;

n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;

as well as their pharmaceutically acceptable salts.

Especially preferred are compounds of formula Ib, in which

R^2 signifies (C_1-C_7)-alkyl or $-NHR^{10}$; and

R^{10} signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl;

R^3 signifies hydrogen or fluoro;

Z has the significances as defined above, wherein R^9 is hydrogen;

R^6 signifies halogen, (C_1-C_7)-alkoxy, (C_1-C_7)-alkylthio, $-O-(CH_2)_m-OR^{11}$, $-O$-fluoro-(C_1-C_7)-alkyl or $-NHR^{12}$; and

R^{12} signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR$ or $-(CH_2)_p-(C_3-C_6)$-cycloalkyl.

More preferred are those compounds of formula 1b, in which

R^2 signifies (C_1-C_7)-alkyl or $-NHR^{10}$;

R^{10} signifies $-(CH_2)_m-OH$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl;

R^3 signifies hydrogen;

R^6 signifies halogen, (C_1-C_7)-alkylthio, $-O-(CH_2)_m-OR^{11}$, $-O$-fluoro-(C_1-C_7)-alkyl or $-NHR^{12}$; and

R^{12} signifies $-(CH_2)_m-OR^{11}$ or $-(CH_2)_p-(C_3-C_6)$-cycloalkyl.

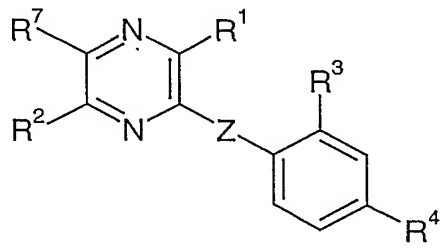
The following are examples of such compounds:

2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,

4-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-

pyrimidine-5-carbonitrile,
4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,
2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,
2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,
4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,
2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile,
2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,
4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidioine-5-carbonitrile,
2-cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,
2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile,
2-(2-hydroxy-ethylamino)-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,
4-chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,
2-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-ethanol, and
2,4-bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile.

Further preferred compounds of formula I in the scope of the present invention are compounds having the general formula



Ic

wherein

R^1 signifies nitro or cyano;

R^2 signifies hydrogen, (C_1-C_7)-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl; and

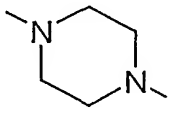
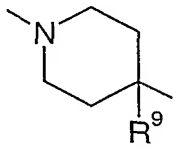
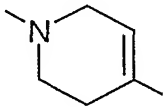
R^{11} signifies hydrogen or (C_1-C_7)-alkyl;

R^3 signifies hydrogen, (C_1-C_7)-alkyl, fluoro, hydroxy, (C_1-C_7)-alkoxy, (C_1-C_7)-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;

R^7 signifies hydrogen, (C_1-C_7)-alkyl or phenyl;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;

m is independently from each other in each occurence 2, 3, 4, 5 or 6;

n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;

as well as their pharmaceutically acceptable salts.

Especially preferred compounds of formula Ic are those, in which R^2 signifies (C_1-C_7)-alkyl or $-NHR^{10}$, R^3 signifies hydrogen or fluoro, Z has the significances as defined above, wherein R^9 is hydrogen; and R^7 signifies (C_1-C_7)-alkyl or phenyl.

More preferred are compounds of formula Ic, in which R^2 signifies (C_1-C_7)-alkyl and R^3 signifies hydrogen.

Examples of such compounds are the following:

4-(4-fluoro-phenyl)-6'-methyl-5'-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile,

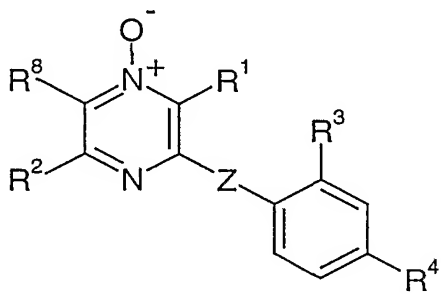
5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile,

6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile,

6-ethyl-5-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile,

5-ethyl-6-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile,
6-ethyl-5-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile,
5-ethyl-6-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile,
5'-ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile, or
6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

Further preferred compounds of formula I in the scope of the invention have the general formula



Id

wherein

R^1 signifies nitro or cyano;

R^2 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $-(CH_2)_m\text{-}OR^{11}$, $-(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl, $-(CH_2)_m\text{-}NH\text{-}C(O)O\text{-}(C_1\text{-}C_7)$-alkyl or $-(CH_2)_p$-pyridyl; and

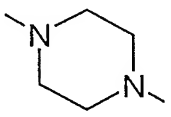
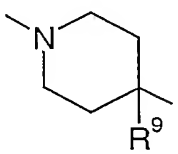
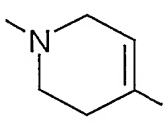
R^{11} signifies hydrogen or $(C_1\text{-}C_7)$-alkyl;

R^3 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, fluoro, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;

R^8 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or phenyl;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;

m is independently from each other in each occurence 2, 3, 4, 5 or 6;

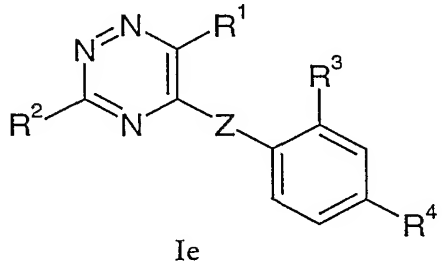
n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;
as well as their pharmaceutically acceptable salts.

Especially preferred compounds of formula Id are those, wherein R^2 signifies (C_1-C_7)-alkyl, R^3 signifies hydrogen or fluoro, Z has the significances as defined above, wherein R^9 is hydrogen, and R^8 signifies (C_1-C_7)-alkyl.

The following are examples of such compounds:
5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile, or
6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile.

Also preferred are compounds of formula I in the scope of the present invention having the general formula



Ie

wherein

R^1 signifies nitro or cyano;

R^2 signifies hydrogen, (C_1-C_7)-alkyl or $-NHR^{10}$; and

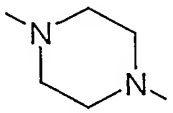
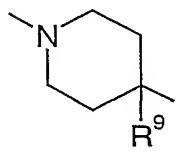
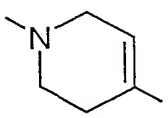
R^{10} signifies hydrogen, (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl; and

R^{11} signifies hydrogen or (C_1-C_7)-alkyl;

R^3 signifies hydrogen, (C_1-C_7)-alkyl, fluoro, hydroxy, (C_1-C_7)-alkoxy, (C_1-C_7)-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;
m is independently from each other in each occurence 2, 3, 4, 5 or 6;
n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and
p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;
as well as their pharmaceutically acceptable salts.

Especially preferred compounds of formula Ie are those, in which R^2 signifies $-NHR^{10}$, R^3 signifies hydrogen and Z has the significances as defined above, wherein R^9 is hydrogen.

3-(2-Hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile is an example of such a compound.

The term "(C_1-C_7)-alkyl" ("lower alkyl") used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, butyl and the like.

The term "(C_2-C_7)-alkenyl" ("lower alkenyl") used in the present description denotes straight-chain or branched unsaturated hydrocarbon residues with 2-7 carbon atoms, preferably with 2-4 carbon atoms. A "(C_2-C_7)-alkenyl" group includes, for example, vinyl, prop-2-enyl, but-3-enyl, pent-4-enyl and isopropenyl.

The term "(C_3-C_6)-cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

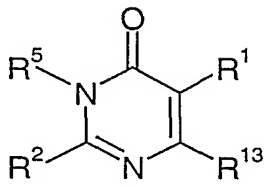
A "fluoro-(C_1-C_7)-alkyl" group is a lower alkyl group as defined above, which is substituted by one or more fluorine atoms, for example trifluoromethyl, 2-fluoroethyl or 2,2,2-trifluoroethyl.

The terms "(C_1-C_7)-alkoxy" or "(C_1-C_7)-alkylthio" denote an lower alkyl group linked to an oxygen or sulphur atom, respectively, wherein the lower alkyl is defined as above. A (C_1-C_7)-alkoxy or a (C_1-C_7)-alkylthio group includes for example methoxy, ethoxy, methylthio or ethylthio.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base.

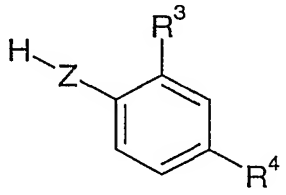
The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by

a) reacting a compound of formula



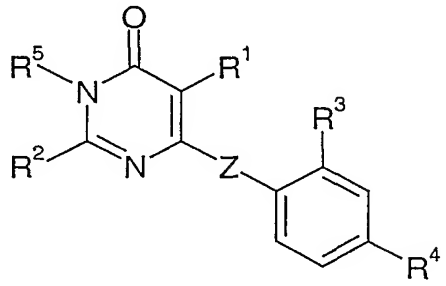
IIa

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

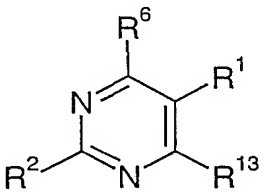


Ia

wherein R^1 to R^5 and Z have the significances as defined before,

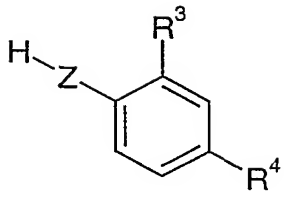
and, if desired, converting a compound of formula Ia into a pharmaceutically acceptable salt; or

b) reacting a compound of formula



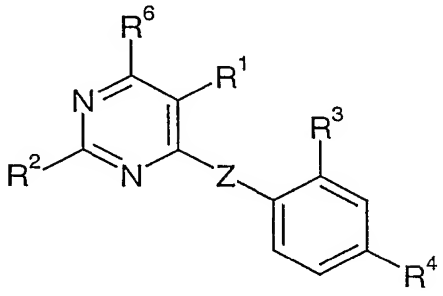
IIb

wherein R^6 and R^{13} signify halogen, with a compound of formula



III

and, if desired, substituting the halogen of R^6 with the resepctive nucleophiles to obtain a compound of formula

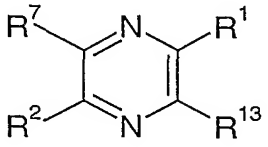


Ib

wherein R^1 to R^4, R^6 and Z have the significances as defined hereinbefore,

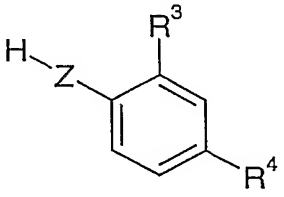
and, if desired, converting a compound of formula Ib into a pharmaceutically acceptable salt; or

c) reacting a compound of formula



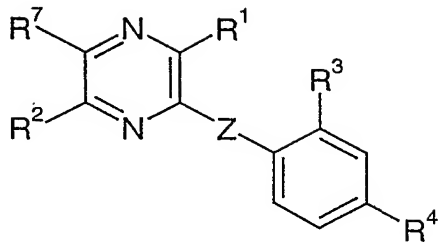
IIc

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

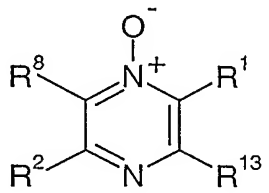


Ic

wherein R^1 to R^4, R^7 and Z have the significances as defined hereinbefore,

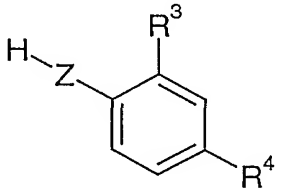
and, if desired, converting a compound of formula Ic into a pharmaceutically acceptable salt; or

d) reacting a compound of formula



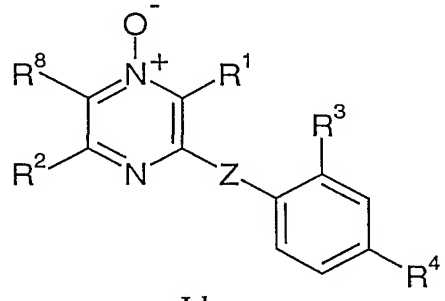
IId

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

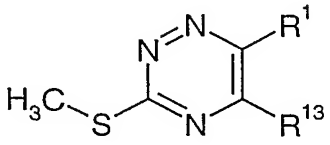


Id

wherein R^1 to R^4, R^8 and Z have the significances as defined hereinbefore,

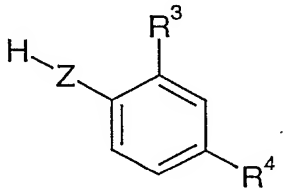
and, if desired, converting a compound of formula Id into a pharmaceutically acceptable salt; or

e) reacting a compound of formula



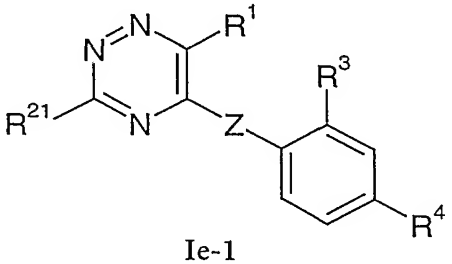
IIe

wherein R^{13} signifies halogen, with a compound of formula



III

and substituting the thiomethyl group with the respective nucleophiles to obtain a compound of formula

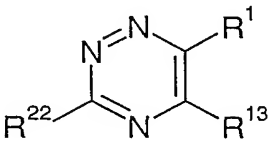


Ie-1

wherein R^{21} signifies $-NHR^{10}$ and R^1, R^3, R^4 and Z have the significances as defined hereinbefore,

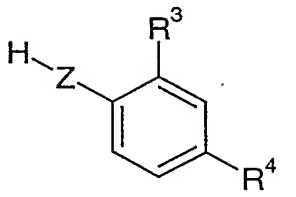
and, if desired, converting a compound of formula Ie-1 into a pharmaceutically acceptable salt; or

f) reacting a compound of formula



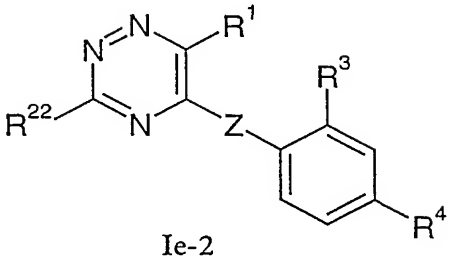
IIf

wherein R^{22} signifies (C_1-C_7)-alkyl and R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula



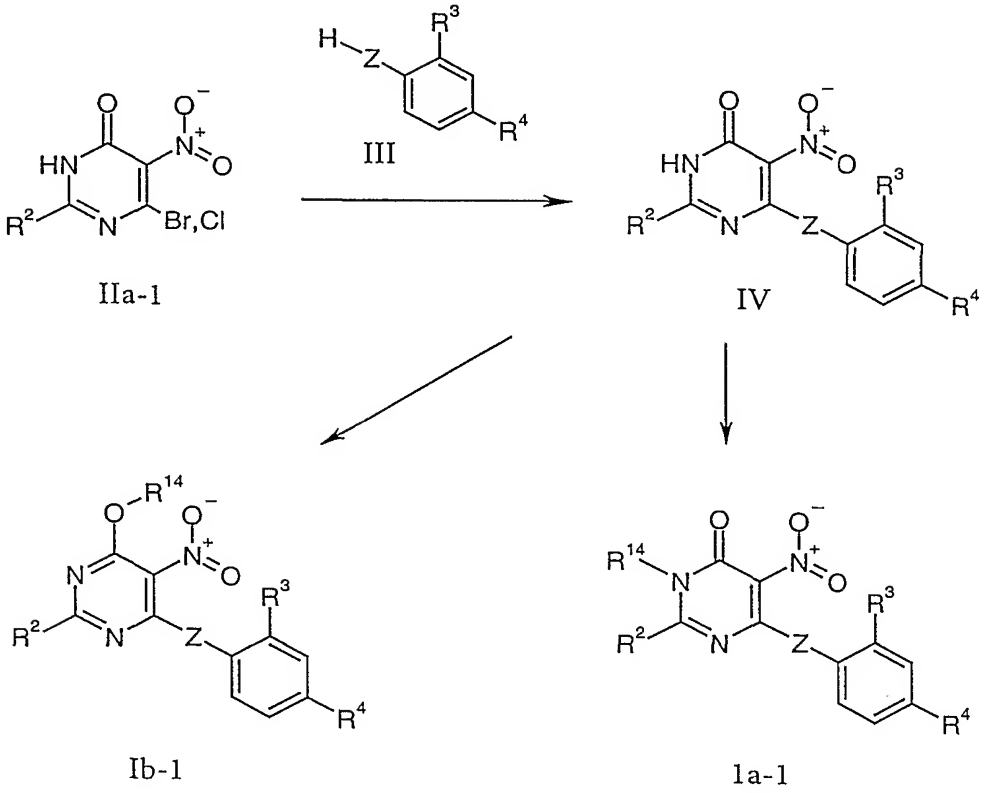
Ie-2

wherein R^{22} signifies (C_1-C_7)-alkyl and R^1, R^3, R^4 and Z have the significances as defined hereinbefore,
and, if desired, converting a compound of formula Ie into a pharmaceutically acceptable salt.

Compounds of general formula Ia and Ib, wherein R^2 signifies (C_1-C_7)-alkyl, can be manufactured by reacting alkyl 6-bromo- or 6-chloro- 5-nitro-3H-pyrimidin-4-ones of general formula IIa-1, e.g. 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one [Eur. Pat. Appl. EP 1 074 549 A2 (2001)], with optionally substituted phenyl-piperazines, phenyl-tetrahydropyridines or phenylpiperidines of general formula III in the presence of a base like potassium carbonate, triethylamine or ethyl-diisopropylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, acetone, methyl-ethylketone or tetrahydrofurane at temperatures between 0 °C and 100 °C to the pyrimidinones IV (Scheme 1). Alkylation of the pyrimidinones IV using optionally substituted alkyl halides, tosylates, mesylates or trifluoro-methansulfonates in solvents like ethanol, methanol, dichloromethane, chloroform, N,N-dimethylformamide, dimethylsulfoxide, acetone, methyl-ethylketone or tetrahydrofurane in the presence of base like alkali carbonates, e.g. sodium, potassium or cesium carbonate, tertiary amines like triethylamine or ethyl-diisopropylamine, alkali metal hydrides, like sodium or potassium hydride, or phase transfer catalysts like benzyl-trimethylammonium chloride in the presence of solid or concentrated aqueous sodium hydroxide gives variable mixtures of N- and/ or O-alkylated compounds Ia-1 and Ib-1 wherein R^{14} signifies (C_1-C_7)-alkyl, -$(CH_2)_m$-OR^{11}, or fluoro-(C_1-C_7)-alkyl. The compounds Ia-1 and Ib-1 may contain functional groups in protected form in the N- or

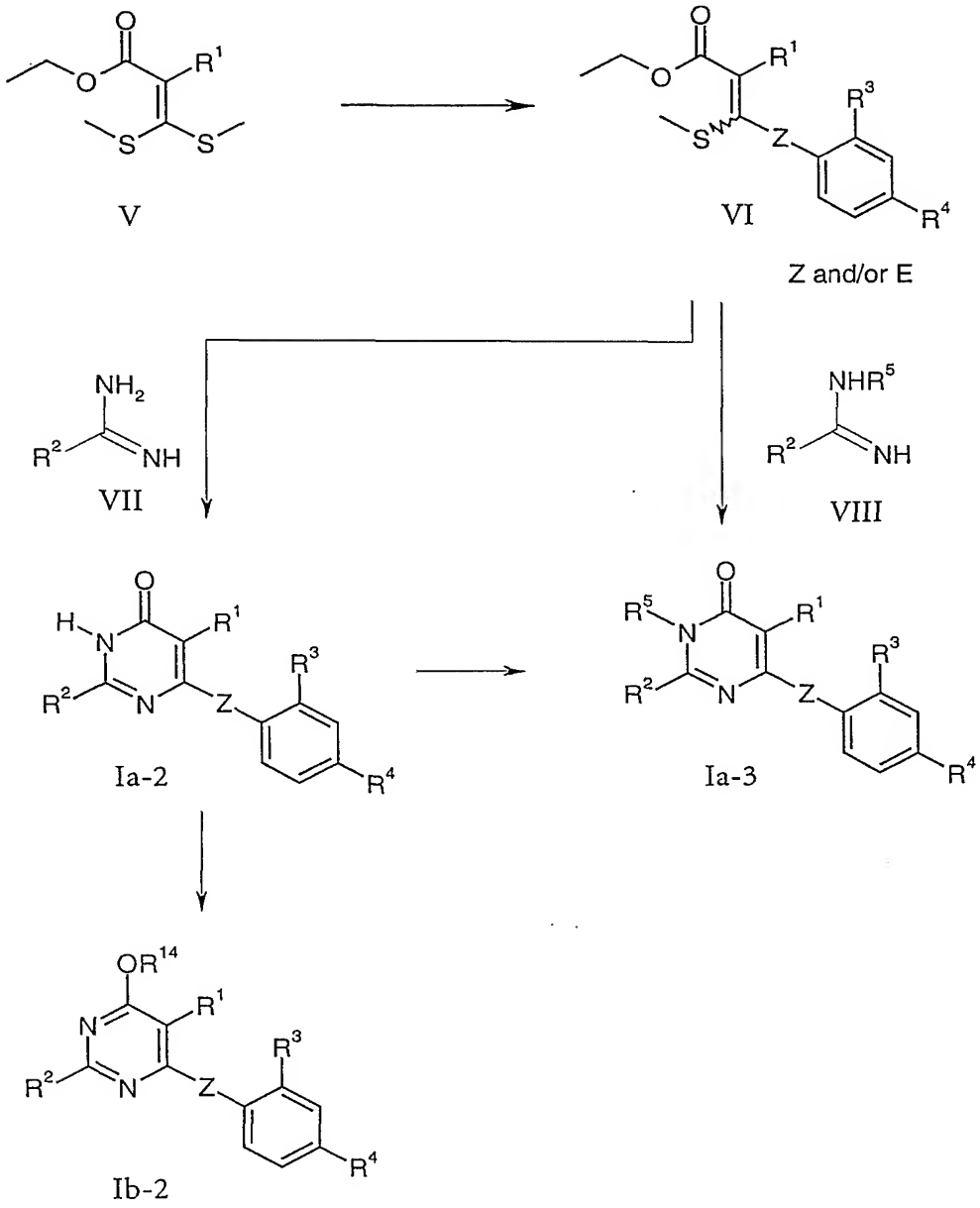
O-alkyl function which allow further structural modifications after removal of the protective functions.

Scheme 1



Known bis(methylthio)-acrylates V react with optionally substituted phenyl-piperazines, phenyl-tetrahydropyridine or phenylpiperidines of general formula III in the presence of bases like potassium carbonate and/or triethylamine in solvents like ethanol, methanol, acetone or methyl-ethylketone at temperatures between room temperature and 100 °C to adducts VI, which can be formed as the Z-isomer, as mixture of the E- and Z-isomers or as the E-isomer [Scheme 2 and Eur. Pat. Appl. EP 1 074 549 A2 (2001)]. Thereupon, adducts VI can be reacted with amidines or urea derivatives of general formula VII or VIII either in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in N,N-dimethylformamide or dimethylsulfoxide at temperatures between 70 °C and 140 °C or in the presence of sodium ethylate in ethanol preferentially at reflux thus yielding pyrimidinones Ia-2 or substituted pyrimidinones Ia-3. Pyrimidinones Ia-2 can then be alkylated as described for the sequence IV => Ia-1 and Ib-1 in Scheme I.

Scheme 2

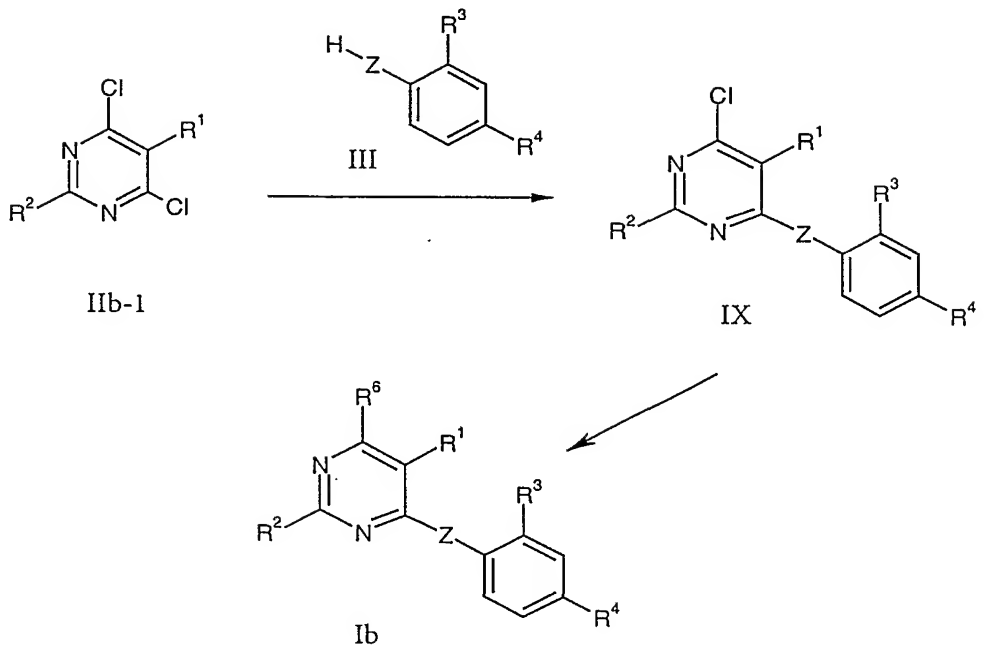


If an allyl moiety is introduced as R^5, then, it can also serve as protective function. Thus, it allows modification at other parts of the molecules, e.g. in R^2 and a later removal of the N-allyl function by lithium borohydride in the presence of palladium(II)acetate and triphenylphosphin in an inert solvent like tetrahydrofuran or 1,2-dimethoxyethane at temperatures between room temperature and 60 °C.

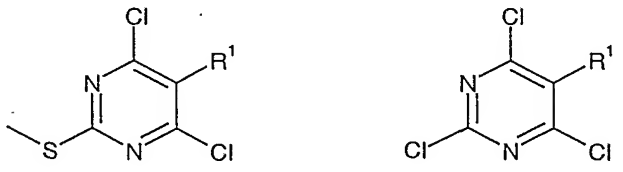
Compounds of general formula Ib can be obtained by sequential substitution of compounds of general formula IIb with the respective nucleophiles. The nucleophilic

substitution reactions can be performed according to known methods, and for the sequence of introduction, the presence of further functionalities in the nucleophile has to be taken into account, a fact generally known to persons skilled in the art. For example, treatment of compounds of general formula IIb-1 with compounds of general formula III via compounds of general formula IX are leading to compounds of general formula Ib. Selective monosubstituion of di-chloro pyrimidines IIb-1 (Scheme 3) with optionally substituted secondary amines III can be performed in solvents like N,N-dimethylform-amide or dimethylsulfoxide in the presence of a base like triethylamine at temperatures between 0 °C and 60 °C producing mono-chloro pyrimidines IX. Thereafter, the remaining chloro atom in compounds IX can be replaced by i) alkoxy functions, treating compounds of formula IX with an alcoholate in the corresponding alcohol as solvent or in an inert solvent like tetrahydrofurane, N,N-dimethylformamide or dimethylsulfoxide at temperatures between room temperature and 100 °C; or by ii) amino functions, treating compounds of formula IX with an amine in an inert solvent like tetrahydrofurane, N,N-dimethylformamide or dimethylsulfoxide at temperatures between room temperature and 100 °C; or by iii) thio functions, treating compounds of formula IX with a thiol in the presence of a base like triethylamine or sodium hydride in an alcohol, N,N-dimethylform-amide or dimethylsulfoxide at temperatures between room temperature and 100 °C. The replacement of the chloro group by a hydroxy function is preferentially performed in a two step prodecure: a 4-methoxy-benzyloxy function is introduced first by reacting IX with the corresponding alcoholate as described above followed by treatment with methanolic hydrogen chloride at temperatures between 0 °C and 50 °C. In case of hydroxy group containing intermediates, these can be protected according to known methods before the treatment with the alcoholates.

Scheme 3



Compounds of general formula IIb-1 wherein R^2 signifies $-NHR^{10}$ can be obtained starting from the 4,6-dichloro-2-methylsulfanyl-pyrimidine derivative X or the 2,4,6-trichloro-pyrimidine derivative XI. Starting with compounds of formula X, they are transformed into the 2-methylsulphonyl derivative according to known oxidative methods, e.g. by 3-chloro-perbenzoic acid in dichloromethane, followed by the treatment with the respective amines in tetrahydrofurane, dioxane, 1,2-dimethoxyethane, N,N-dimethylformamide or dimethylsulfoxide at temperatures between room temperature and about 100 °C to yield compounds of general formula IIb-1.



In case, compounds of formula XI are selected as starting materials, the treatment with amines in tetrahydrofurane, dioxane, 1,2-dimethoxyethane, ethanol, N,N-dimethyl-formamide or dimethylsulfoxide, at temperatures between room temperature and about 100 °C, in presence of a base, e.g. potassium carbonate, triethylamine or ethyl-diisopropyl-amine yields the 2- and 4-substituted derivatives. These can be separated by chromato-graphic methods and identified by physical methods known as such like ^{13}C-

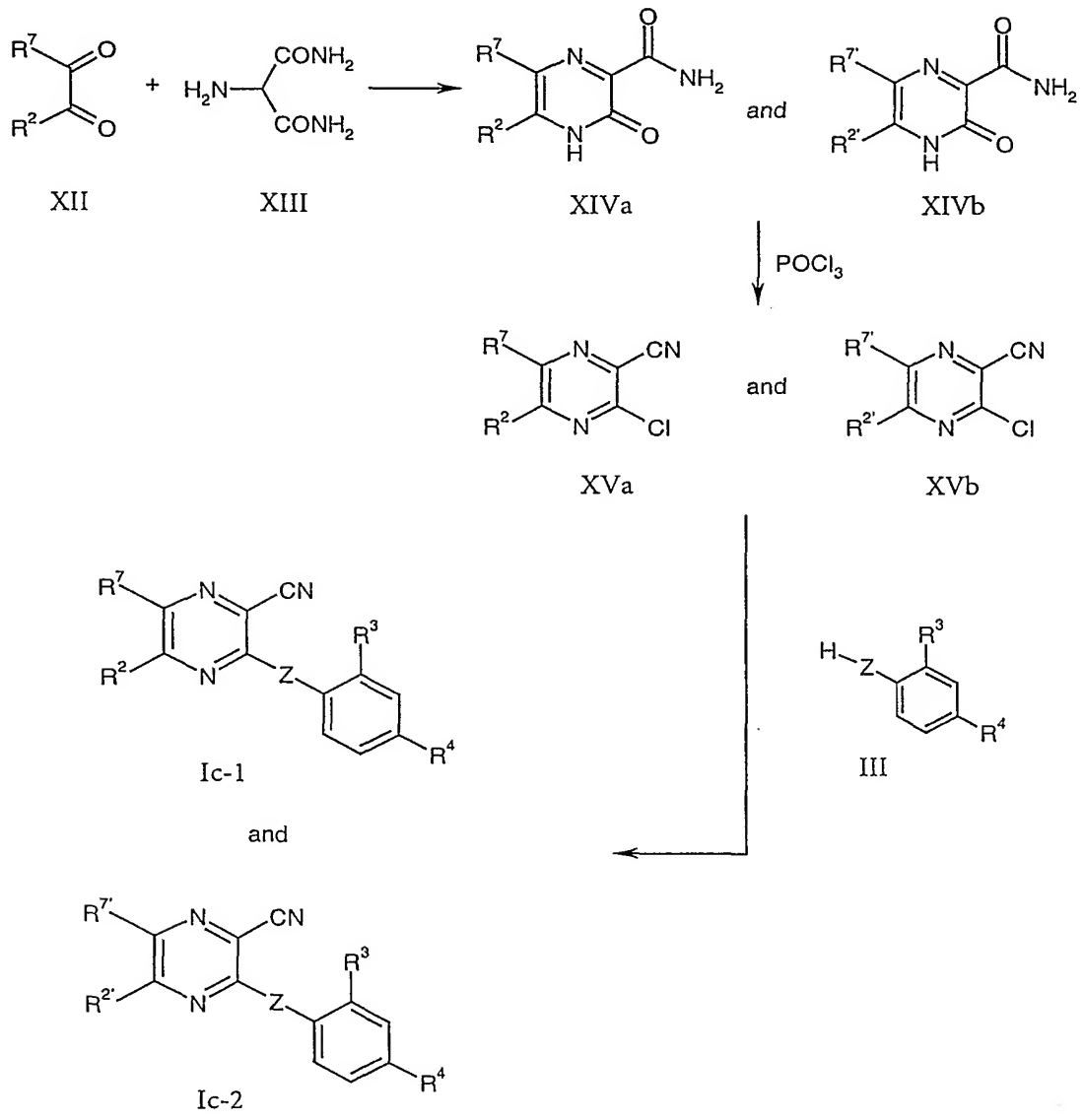
NMR or X-ray analysis; e.g. when R^2 signifies hydroxyethylamino the assignment was performed by X-ray analysis.

When an excess of the nucleophile is used under the aforementioned conditions, the 2,4-disubstituted derivative can be obtained.

To obtain compounds of general formula Ic, 1,2-dicarbonyl compounds XII with R^2 and R^7 signifying both independently from each other hydrogen, phenyl, (C_1-C_7)-alkyl or (C_2-C_7)-alkenyl, react with 2-amino-malonic acid diamide XIII as described in *J. Amer. Chem. Soc.* 1949, 71, 78-81, either in the presence of an aqueous base at temperatures between 0 °C and 60 °C or in the absence of a base in solvents like water or an alcohol at temperatures between room temperature and 120 °C to form the 3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amides XIVa and XIVb, in which the former substituent R^2 of the 1,2-dicarbonyl compounds XII became the substituent $R^{7'}$ and the former substituent R^7 in the 1,2-dicarbonyl compounds XII became the substituent $R^{2'}$. Treatment of XIVa and XIVb either separately or as a mixture with phosphorus oxychloride and optionally additional phosphorus pentachloride in the presence of triethylamine or diethylaniline at temperatures between 40 °C and 120 °C give 3-chloro-pyrazine-2-carbonitriles XVa and XVb (Scheme 4).

3-Chloro-pyrazine-2-carbonitriles XVa and XVb react either separately or as a mixture with optionally substituted phenyl-piperazines, phenyl-tetrahydropyridines or phenyl-piperidines or their hydrochlorides in solvents like N,N-dimethylformamide, acetonitrile, acetone or dimethylsulfoxide in the presence of a base like potassium carbonate or a tertiary amine as diisopropyl-ethylamine at temperatures between room temperature and 80 °C to form the desired 3-(phenyl-piperazine-yl, phenyl-tetrahydro-pyridine-yl or phenylpiperidine-yl)-pyrazine-2-carbonitriles Ic-1 and Ic-2 which can be separated by known methods such as chromatography or crystallization.

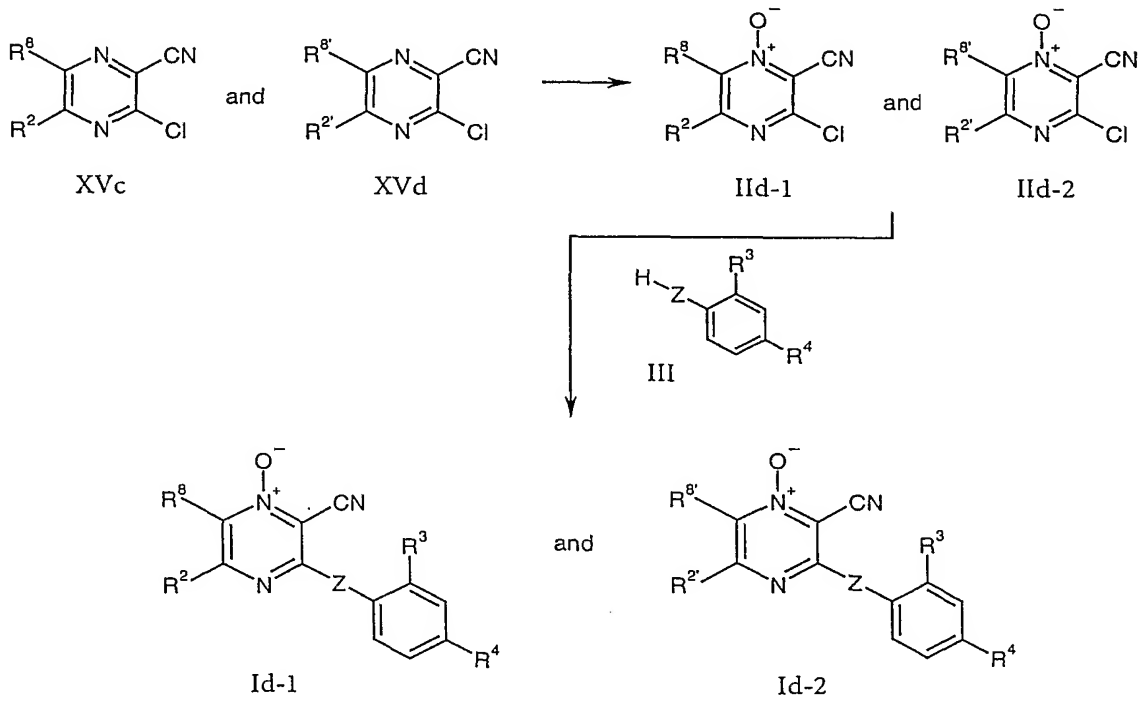
Scheme 4



To obtain compounds of general formula Id, 3-chloro-pyrazine-2-carbonitriles XVc and XVd can be oxidized to the corresponding mono-oxy-pyrazine compounds by various methods. If hydrogen peroxide in a solvent like trifluoroacetic acid is used preferentially at temperatures between 0 °C and 60 °C, then mainly 1-oxy-pyrazine-2-carbonitriles IId-1 and IId-2 are formed (Scheme 5). 1-Oxy-pyrazine-2-carbonitriles IId-1 and IId-2 react either separately or as a mixture with optionally substituted phenyl-piperazines, phenyl-tetrahydropyridines or phenylpiperidines or their hydrochlorides in solvents like N,N-dimethylformamide, acetonitrile, acetone or dimethylsulfoxide in the presence of a base like potassium carbonate or a tertiary amine as diisopropyl-ethylamine at temperatures between room temperature and 80 °C to form the desired 3-(phenyl-

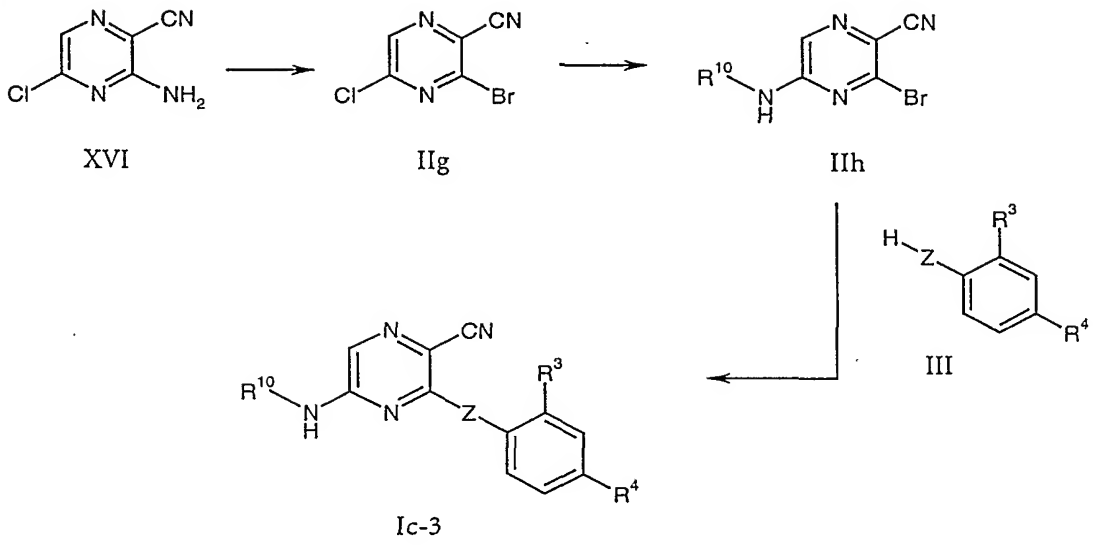
piperazine-yl, phenyl-tetrahydropyridine-yl or phenylpiperidine-yl) 1-oxy-pyrazine-2-carbonitriles Id-1 and Id-2 which can be separated by known methods such as chromatography or crystallization.

Scheme 5

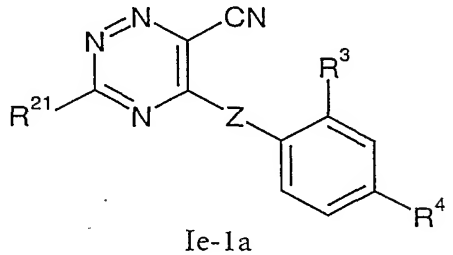


The diazotization of the 3-amino-5-chloro-2-cyano-pyrazine XVI according to *J.Org.Chem.* 1975, 40, 2341-2347, with t-butyl-nitrite in solvents like acetonitrile or N,N-dimethylformamide in the presence of copper-(II)-bromide at temperatures between room temperature and 95 °C gives the 3-bromo-5-chloro-2-cyano-pyrazine IIg. The 3-bromo-5-chloro-2-cyano-pyrazine IIg reacts with one equivalent of a primary or secondary amine to two products, in which either the chloro-atom or the bromo-atom is replaced in the amine moiety. If the reaction is performed with a primary amine $R^{10}NH_2$ in a solvent like dioxane or tetrahydrofurane in the presence of a base like triethylamine or diisopropylethylamine, preferentially at room temperature, then the pyrazine IIh with replaced chloro-atom can be obtained with reasonable selectivity. In a second analogous reaction, optionally substituted phenyl-piperazines, phenyl-tetrahydro-pyridines or phenylpiperidines or their hydrochlorides can then be reacted with the pyrazine IIh in solvents like N,N-dimethylformamide, tetrahydrofurane, dioxane, acetonitrile, acetone or dimethylsulfoxide and in the presence of a base like potassium carbonate or a tertiary amine like diisopropyl-ethylamine at temperatures between room temperature and 80 °C giving compounds of general formula Ic-3 wherein R^7 signifies hydrogen (Scheme 6).

Scheme 6

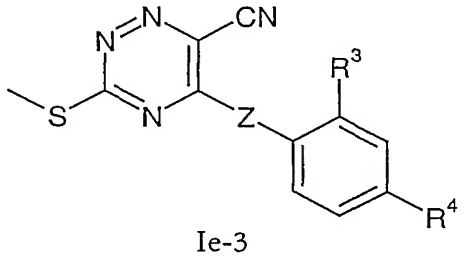


Compounds of general formula Ie-1a



Ie-1a

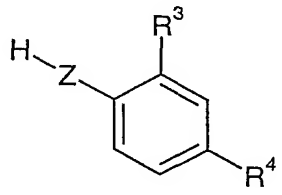
wherein R^{21} signifies $-NHR^{10}$, can be obtained by reacting compounds of formula Ie-3



Ie-3

with appropriate nucleophiles. Substitution of the Me-S-group in compound Ie-3 by optionally substituted N-nucleophiles can be performed in water, ethanol, N,N-dimethylformamide, dimethylsulfoxide, 1,2-dimethoxyethane, preferentially in dioxane at elevated temperatures, preferentially 100 °C to 160 °C.

Compounds of formula Ie-3 are prepared by reaction of 1, 3-(methylthio)-5-chloro-6-cyano-1,2,4-triazine (J.J.Huang, *J.Org.Chem.* 1985, 50, 2293-2298) with amines of general formula III

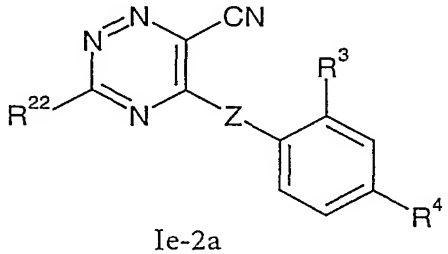


III

in the presence of a base like triethylamine or ethyl-diisopropylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, methyl-ethylketone, ethanol, dioxane or tetrahydrofuran at temperatures between 10 °C and 50 °C.

The functionalization of the N-nucleophiles can also serve as a protective function. Thus, modifications at the other part of the R^{21}-substituent are allowed, e.g. removal of a N-protecting group, like the tert-butoxycarbonyl group, by methods well documented in the literature.

Compounds of general formula Ie-2a

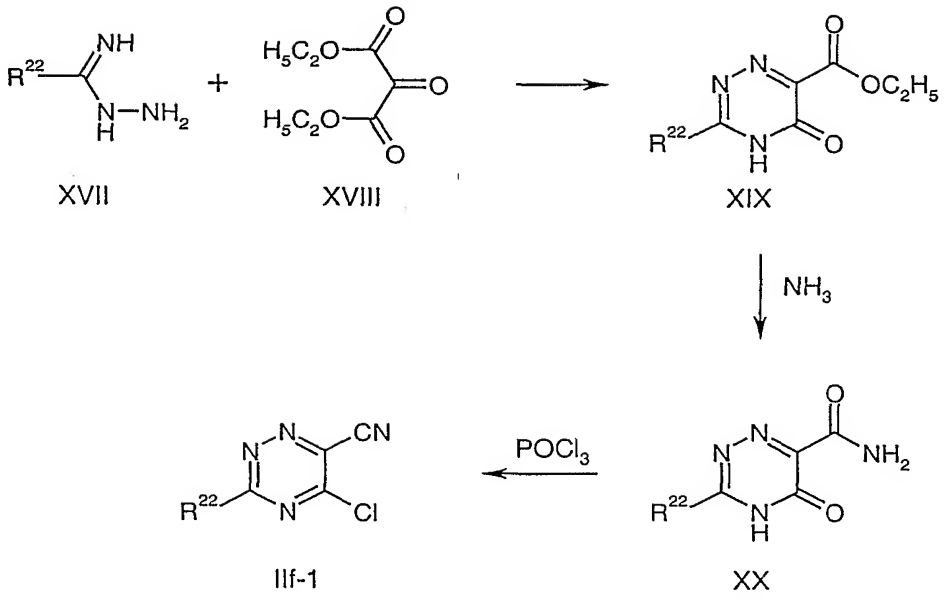


Ie-2a

wherein R^{22} signifies (C_1-C_7)-alkyl can be prepared by reacting the intermediate IIf-1 with amines of general formula III in the presence of a base like triethylamine or ethyl-diisopropylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, methyl-ethylketone, ethanol, dioxane or tetrahydrofurane at temperatures between 10 °C and 50 °C.

The intermediate IIf-1 can be synthesized in analogy to the procedure described in *J.Org.Chem.* 1972, 37 (24), 3958-3960, starting with the condensation of the corresponding amidrazones XVII and methyl or ethyl oxomalonate XVIII , followed by ammonolysis of the ester XIX, and, finally, dehydration of the amide XX and substitution of the hydroxy group by chlorine (Scheme 7).

Scheme 7



The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds of formula I.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits and psychosis. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary

incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

The compounds of the present invention are group I mGluR antagonists. Their pharmacological activity was tested using the following method:

Binding assay for the characterization of mGluR 1 antagonistic properties

Binding assay with tritiated 1-ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile: HEK 293 cells were transiently transfected with the rat mGluR1a receptor. The cells were collected and washed 3 times with PBS. The cell pellets were frozen at –80 °C. Membranes were prepared from HEK 293 cells transfected with the rat mGluR1a receptor and used in the binding experiments at 10 µg proteins per assay after resuspension in a HEPES NaOH 20mM, pH=7.4 binding buffer. 1-Ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile (S.A 33.4 Ci/mmol) was used at 3 nM final concentration. The incubation with variable concentrations of potential inhibitors was performed for 1 hour at room temperature, the incubate was then filtered onto GF/B glass fiber filter preincubated 1 hour in PEI 0,1% and washed 3 times with 1ml of cold binding buffer. The radioactivity retained on the unifilter 96 was counted using a Topcount β counter. After correction for non specific binding the data were normalized and the IC_{50} value calculated using a 4 parameters logistic equation which was fitted to the inhibition curve.

The preferred compounds have an IC_{50} range of 0.001 – 10.0 µmol/l.

In the table below are shown some specific IC_{50} values of preferred compounds of formula I of the present invention as measured with the binding assay described above:

Compound name	Example No.	IC_{50} (µmol/l))
6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one	1	0.81
2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3H-pyrimidin-4-one	5	0.063
6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-3-(2-hydroxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one	8-1	0.042
2-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-ethanol	8-2	0.058
3-ethyl-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one	10-1	0.049
4-ethoxy-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidine	10-2	0.18

Compound name	Example No.	IC_{50} (μmol/l))
6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-3-(4-hydroxy-butyl)-2-methyl-5-nitro-3H-pyrimidin-4-one	18	0.28
4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile	20	0.290
2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-methylsulfanyl-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile	25	0.350
2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-nitro-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile	29	0.75
4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile	32	0.700
4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile	35	0.390
4-(4-cyano-4-phenyl-piperidin-1-yl)-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile	37	1.8
2,4-bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile	38	0.064
4-(4-phenyl-piperazin-1-yl)-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile	40	1.50
2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile	47	0.033
4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile	49	0.15
4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile	54	0.030
2-(2-hydroxy-ethylamino)-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile	60	0.036
4-chloro-2-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile	63	0.025
4-chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile	68	0.140
2-amino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile	70	0.210
2-amino-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile	73	0.159
5'-ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile	75-1	0.017
6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile	75-2	0.023
5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile	79-1	0.025
6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile	79-2	0.21
4-(4-fluoro-phenyl)-6'-(2-hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile	83	1.0
3-(2-hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile	84	0.66

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/

kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind, is also an object of the invention.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one

0.791 g (6.0 mmol) of N-ethyldiisopropylamine were slowly added to a solution of 0.468 g (2.00 mmol) of the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared according to Eur. Pat. Appl. EP 1 074 549 A2) and 0.441 g (2.40 mmol) of the 1-(4-fluoro-phenyl)piperazine in 20 ml of N,N-dimethylformamide. The reaction mixture was stirred at room temperature for 16 hours. It was then poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue obtained was then recrystallised from an ethylacetate/hexane mixture. There was thus obtained 0.570 g (1.71 mmol, 85.5 % of theory) of the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as yellow solid; m.p. >250 °C (decomposition); MS: $[M+H]^+ = 334$.

Example 2

6-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared in Eur. Pat. Appl. EP 1 074 549 A2) was treated with the (2-fluoro-phenyl)-piperazine in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield the 6-[4-(2-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as yellow amorphous solid; MS: $[M+H]^+ = 334$.

Example 3

6-(4-Hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared in Eur. Pat. Appl. EP 1 074 549 A2) was treated with the 4-hydroxy-4-phenylpiperidine in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield the 6-(4-hydroxy-4-phenyl-piperidin-1-yl)-2-methyl-5-nitro-3H-pyrimidin-4-one as yellow solid; m.p. >250 °C (decomposition); MS: $[M+H]^+ = 331$.

Example 4

2-Methyl-5-nitro-6-(4-phenyl-piperazin-1-yl)-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared in Eur. Pat. Appl. EP 1 074 549 A2) was treated with the 1-phenylpiperazine in N,N-dimethylformamide in the presence of potassium carbonate at room temperature to yield the 2-methyl-5-nitro-6-(4-phenyl-piperazin-1-yl)-3H-pyrimidin-4-one as yellow solid; m.p. >250 °C (decomposition); MS: $[M-H]^-$ = 314.

Example 5

2-Methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared in Eur. Pat. Appl. EP 1074549 A2) was treated with the 4-phenylpiperidine in N,N-dimethylformamide in the presence of N-ethyldiisopropyl-amine at room temperature to yield the 2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3H-pyrimidin-4-one as yellowish solid; m.p. 210-213 °C; MS: $[M+H]^+$ = 315.

Example 6

2-Methyl-5-nitro-6-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (prepared as in Eur. Pat. Appl. EP 1 074 549 A2) was treated with the 1,2,3,6-tetrahydro-4-phenylpiperidine hydrochloride in N,N-dimethylformamide in the presence of N-ethyldiisopropylamine at room temperature to yield the 2-methyl-5-nitro-6-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-3H-pyrimidin-4-one as yellowish solid; m.p. 212-216 °C (decomposition); MS: $[M+H]^+$ = 313.

Example 7

6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy to the procedure described in example 1, the 6-bromo-2-methyl-5-nitro-3H-pyrimidin-4-one (as prepared in Eur. Pat. Appl. EP 1 074 549 A2) was treated with the 4-(4-fluoro-phenyl)-piperidine hydrochloride in N,N-dimethylformamide in the presence of N-ethyldiisopropylamine at room temperature to yield the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as yellowish solid; m.p. 218-221 °C (decomposition); MS: $[M-H]^-$ = 331.

Example 8

6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-3-(2-hydroxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one

and

2-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-ethanol

0.180 g (0.540 mmol) of the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1) and 0.142 g (1.1 mmol) of N-ethyldiisopropylamine, dissolved in 5.0 ml of N,N-dimethylformamide, were slowly added between –5 °C and 0 °C to a suspension of 0.923 g (7.0 mmol) of 2-bromo-ethanol and 0.897 g (6.5 mmol) of potassium carbonate in 5.0 ml of N,N-dimethylformamide. The reaction mixture was then stirred at room temperature for 48 hours. It was then poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 9:1 to 1:1 v/v gradient of hexane and ethylacetate as the eluent giving 0.039 g (0.10 mmol, 19.1% of theory) of the 2-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-ethanol as a light yellow amorphous solid; MS: $[M+H]^+ = 378$; and 0.091 g (0.241 mmol, 44.7% of theory) of the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-3-(2-hydroxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one as yellowish amorphous solid; MS: $[M+H]^+ = 378$.

Example 9

2-Methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one

and

2-methyl-5-nitro-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine

0.591 g (2.55 mmol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate were added slowly at room temperature to a suspension of 0.200 g (0.636 mmol) of the 2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3H-pyrimidin-4-one (example 5) and 0.135 g (1.27 mmol) of sodium carbonate in 5.0 ml of acetone. After stirring of the reaction mixture for 2 hours, 0.136 g (0.99 mmol) of potassium carbonate were added and stirring continued for 18 hours. Additional 0.296 g (1.27 mmol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate were added and stirring continued for 4 hours. The reaction mixture was then poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane.

The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 9:1 to 1:1 v/v gradient of hexane and ethylacetate as the eluent giving 0.077 g (0.194 mmol, 30.5% of theory) of the 2-methyl-5-nitro-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine as a light yellow solid; m.p. 114-117 °C; MS: $[M+H]^+$ = 397; and 0.166 g (0.419 mmol, 65.8% of theory) of the 2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one as yellowish solid; m.p. 161-163 °C; MS: $[M+H]^+$ = 397.

Example 10

3-Ethyl-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one

and

4-ethoxy-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidine

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1) was treated with ethyliodide and potassium carbonate in N,N-dimethylformamide at room temperature to yield the 4-ethoxy-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidine as a light yellow solid; m.p. 116-119 °C; MS: $[M+H]^+$ = 362; and the 3-ethyl-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as yellowish solid; m.p. 126-128 °C; MS: $[M+H]^+$ = 362.

Example 11

4-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-6-isopropoxy-2-methyl-5-nitro-pyrimidine

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1) was treated with 2-bromo-propane, potassium iodide and potassium carbonate in N,N-dimethylformamide at 80 °C to yield the 4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-isopropoxy-2-methyl-5-nitro-pyrimidine as a light yellow solid; m.p. 98-100 °C; MS: $[M+H]^+$ = 376.

Example 12

6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one

and

4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-6-(2,2,2-trifluoro-ethoxy)-pyrimidine

In analogy to the procedure described in example 9, the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1) was treated with 2,2,2-trifluoroethyl trifluoromethanesulfonate, sodium and potassium carbonate in acetone at room temperature to yield the 4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-6-(2,2,2-trifluoro-ethoxy)-pyrimidine as a light brown solid; m.p. 92-95 °C; MS: $[M+H]^+ = 416$; and the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one as yellow amorphous solid; MS: $[M+H]^+ = 416$.

Example 13

6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one

and

4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-6-(2,2,2-trifluoro-ethoxy)-pyrimidine

In analogy to the procedure described in example 9, the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 7) was treated with 2,2,2-trifluoro-ethyl trifluoromethanesulfonate, sodium and potassium carbonate in acetone at room temperature to yield the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-6-(2,2,2-trifluoro-ethoxy)-pyrimidine as a yellow oil; MS: $[M+H]^+ = 415$; and the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one as yellow solid; m.p. 61-64 °C; MS: $[M+H]^+ = 415$.

Example 14

6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-3-(2-methoxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one

and

4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-methoxy-ethoxy)-2-methyl-5-nitro-pyrimidine

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 7) was treated with 2-bromoethyl methyl ether and potassium carbonate in N,N-dimethylformamide at 50 °C to yield the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-methoxy-ethoxy)-2-methyl-5-nitro-pyrimidine as a yellow oil; MS: $[M+H]^+ = 391$; and the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-3-(2-methoxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one as a yellow solid; m.p. 45-48 °C; MS: $[M+H]^+ = 391$.

Example 15

6-{6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-hexan-1-ol

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 1) was treated with 6-chloro-1-hexanol and potassium carbonate in N,N-dimethylformamide at 120 °C to yield the 6-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-hexan-1-ol as a yellow amorphous solid; MS: $[M+H]^+ = 434$.

Example 16

{4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-6-oxo-6H-pyrimidin-1-yl}-acetonitrile

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 7) was treated with bromo-acetonitrile and potassium carbonate in N,N-dimethylformamide at room temperature to yield the {4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-6-oxo-6H-pyrimidin-1-yl}-acetonitrile as a yellow solid; m.p. 213-215 °C (decomposition); MS: $[M+H]^+ = 372$.

Example 17

4-{6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-butan-1-ol

a) 3-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one and 4-[4-(tert-butyl-dimethyl-silanyloxy)-butoxy]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidine

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 7) was treated with tert.-butyl-(4-chlorobutoxy)dimethylsilane and potassium carbonate in N,N-dimethyl-formamide at 80 °C to yield the 4-[4-(tert-butyl-dimethyl-silanyloxy)-butoxy]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidine as a yellowish oil; MS: $[M+H]^+ = 519$; and the 3-[4-(tert-butyl-dimethyl-silanyloxy)-butyl]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as a yellowish oil; MS: $[M+H]^+ = 519$.

b) 4-{6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-butan-1-ol

0.590 g (14.5 mmol) of hydrofluoric acid (47-51% in water) were slowly added to a solution of 0.375 g (0.723 mmol) of the 4-[4-(tert-butyl-dimethyl-silanyloxy)-butoxy]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidine in 10.0 ml of acetonitrile and 5.0 ml of dichloromethane. The reaction mixture was then stirred at room temperature for 1 hour. It was then poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 9:1 to 1:1 v/v gradient of hexane and ethylacetate as the eluent giving 0.181 g (0.448 mmol, 61.9% of theory) of the 4-{6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-butan-1-ol as a light yellowish oil; MS: $[M+H]^+ = 405$.

Example 18

6-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-3-(4-hydroxy-butyl)-2-methyl-5-nitro-3H-pyrimidin-4-one

In analogy the procedure described in example 17b, the 3-[4-(tert-butyl-dimethyl-silanyloxy)-butyl]-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-

pyrimidin-4-one (example 17a) was treated with hydrofluoric acid (47-51% in water) in acetonitrile and dichloromethane at room temperature to yield the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-3-(4-hydroxy-butyl)-2-methyl-5-nitro-3H-pyrimidin-4-one as a yellow solid; m.p. 154-156 °C; MS: $[M+H]^+ = 405$

Example 19

3-(2-Ethoxy-ethyl)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one

and

4-(2-ethoxy-ethoxy)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidine

In analogy to the procedure described in example 8, the 6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one (example 7) was treated with 2-bromoethyl ethyl ether and potassium carbonate in N,N-dimethylformamide at 80 °C to yield the 4-(2-ethoxy-ethoxy)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidine as a yellow oil; MS: $[M+H]^+ = 406$; and the 3-(2-ethoxy-ethyl)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one as a yellow oil; MS: $[M+H]^+ = 406$.

Example 20

4-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

a) 4-Chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

A solution of 10.0 g (48 mmol) of 2,4,6-trichloro-5-cyano-pyrimidine in 150 ml of dioxane was treated at 0 °C with 16.4 ml (96 mmol) of N-ethyl-diisopropylamine, followed by 8.7 ml (144 mmol) of ethanolamine. While warming up to room temperature, yellowish solid material started to precipitate. The yellow solution was stirred overnight, then the resulting material was separated by filtration and the mother liquor evaporated to dryness. The residue was stirred with dichloromethane and the solid filtered. To eliminate the ethanolammonium chloride, the two combined solid fractions were treated with 100 ml of ethanol, thereupon the resulting product was washed with 150 ml of dichloromethane. After drying under reduced pressure, 10.45 g (40.6 mmol, 84.5 % of theory) of 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile were obtained as a yellowish powder.

b) 4-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

A mixture of 125 mg (0.48 mmol) of 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile and 63 mg (0.48 mmol) of N-ethyl-diisopropylamine in 5 ml of ethanol was treated with 97 mg (0.48 mmol) of 1-(2-fluorophenyl)-piperazine. The solution was heated at 80 °C during 15 h, and, thereafter, evaporated under reduced pressure. To separate the unreacted starting material, the residue obtained was then chromatographed on silica gel using a 95:15:0.1 mixture of dichloromethane, methanol and ammonium hydroxide as the eluent giving 70 mg (0.17 mmol, 36 % of theory) of the 4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 402$.

Example 21

4-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with the 1-(4-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as a white lyophilisate; MS: $[M+H]^+ = 402$.

Example 22

4-[4-(2-Cyano-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-cyanophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 50 °C to yield 4-[4-(2-cyano-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M]^+ = 408$.

Example 23

2,4-Bis-(2-hydroxy-ethylamino)-6-(4-o-tolyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(o-tolyl)-piperazine dihydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at 80 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-(4-o-tolyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 398$.

Example 24

4-[4-(2-Ethyl-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-ethyl-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 4-[4-(2-ethyl-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 412$.

Example 25

2,4-Bis-(2-hydroxy-ethylamino)-6-[4-(2-methylsulfanyl-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-methylsulfanyl-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield the 2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-methylsulfanyl-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile as a yellowish lyophilisate; MS: $[M+H]^+ = 430$.

Example 26

2,4-Bis-(2-hydroxy-ethylamino)-6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-methoxy-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield the

2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-methoxy-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile as a yellowish lyophilisate; MS: $[M+H]^+ = 414$.

Example 27

4-[4-(2-Ethoxy-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-ethoxy-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 4-[4-(2-ethoxy-phenyl)-piperazin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as a white lyophilisate; MS: $[M+H]^+ = 428$.

Example 28

2,4-Bis-(2-hydroxy-ethylamino)-6-[4-(2-hydroxy-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-hydroxy-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-hydroxy-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile as a white lyophilisate; MS: $[M+H]^+ = 399$.

Example 29

2,4-Bis-(2-hydroxy-ethylamino)-6-[4-(2-nitro-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-(2-nitro-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-nitro-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile as a yellowish lyophilisate; MS: $[M+H]^+ = 429$.

Example 30

2,4-Bis-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-phenyl-piperazine in N,N-dimethylformamide in the presence of N-ethyl-diisopropylamine at 40 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, colorless solid; MS: $[M+H]^+ = 384$.

Example 31

2,4-Bis-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-phenyl-piperidine in ethanol in the presence of N-ethyl-diisopropylamine at 80 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 383$.

Example 32

4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-(4-fluorophenyl)-piperidine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 401$.

Example 33

2,4-Bis-(2-hydroxy-ethylamino)-6-[4-(2-methoxy-phenyl)-piperidin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-(2-methoxy-phenyl)-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-[4-(2-methoxy-phenyl)-piperidin-1-yl]-pyrimidine-5-carbonitrile as a white lyophilisate; MS: $[M+H]^+ = 413$.

Example 34

2,4-Bis-(2-hydroxy-ethylamino)-6-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-phenyl-1,2,3,6-tetrahydro-pyridine hydrochloride in ethanol in the presence of N-ethyl-diisopropylamine at 80 °C to yield 2,4-bis-(2-hydroxy-ethylamino)-6-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, brown solid; MS: $[M+H]^+ = 381$.

Example 35

4-[4-(4-Fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride in dioxane in the presence of N-ethyl-diisopropyl-amine at 90 °C to yield 4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 399$.

Example 36

4-[4-(4-Fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20 (2), the 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with the 4-(4-fluorophenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at 60°C to yield the 4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS : $[M+H]^+ = 399$.

Example 37

4-(4-Cyano-4-phenyl-piperidin-1-yl)-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 4-phenyl-piperidine-4-carbonitrile in dioxane in the presence of N-ethyl-diisopropylamine at 60 °C to yield 4-(4-cyano-4-phenyl-piperidin-1-yl)-2,6-bis-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 408$.

Example 38

2,4-Bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 2,4,6-Trichloro-5-cyano-pyrimidine

The starting material, 2,4,6-trichloro-5-cyano-pyrimidine, was prepared in analogy to the procedure described for 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile [J. Heterocycl. Chem. (1971), 8(5), 445-453] as follows:

(i) 2,4,6-Trichloro-pyrimidine-5-carbaldehyde

To 179.2 ml (1.96 mol) of phosphoryl chloride were added 23.2 ml (0.30 mol) of N,N-dimethylformamide at 0 °C within 20 min. Thereupon, portionwise, 38.6 g (0.30 mol) of barbituric acid were added to the white suspension within 30 min. The reaction mixture was warmed up to room temperature and then heated to 100 °C during 15 h. For the working-up, the brownish solution was evaporated under reduced pressure and the resulting residue hydrolyzed on 700 ml of ice-water. The aqueous phase was extracted altogether with 3500 ml of tert-butyl-methyl ether, then the combined organic phases were dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was stirred with ether to yield 28.4 g (0.13 mol, 44.5% of theory) of 2,4,6-trichloro-pyrimidine-5-carbaldehyde as a yellow powder. Additional 2.9 g (0.013 mol, 4.6% of theory) of the product were obtained by concentrating the etheric solution. The quality of the product was sufficient to be used in the next step without further purification.

(ii) (E/Z)-2,4,6-Trichloro-pyrimidine-5-carbaldehyde oxime

A solution of 8.76 g (0.041 mol) of 2,4,6-trichloro-pyrimidine-5-carbaldehyde in 109.4 ml of acetic acid and 5.5 ml of water was treated at room temperature with 2.88 g (0.041

mol) of hydroxylamine hydrochloride. Thereafter, the mixture was warmed to 60 °C during 25 min. For the working-up, the red solution was cooled to room temperature and poured into 300 ml of a mixture of ice and water. The aqueous phase was extracted three times with 250 ml of dichloromethane. The combined organic phases were washed two times with a saturated aqueous solution of sodium chloride, then dried over sodium sulfate, and evaporated under reduced pressure to yield 8.03 g (0.035 mol, 85% of theory) of (E/Z)-2,4,6-trichloro-pyrimidine-5-carbaldehyde oxime as an orange solid which was used in the next step without further purification.

(iii) 2,4,6-Trichloro-5-cyano-pyrimidine

A solution of 8.03 g (0.035 mol) of (E/Z)-2,4,6-trichloro-pyrimidine-5-carbaldehyde oxime in 85 ml of thionylchloride prepared at 0 °C, was heated to room temperature, then, during 2 hours to reflux. For the working-up, the yellow reaction mixture was cooled to room temperature, then evaporated under reduced pressure to yield 7.57 g of crude 2,4,6-trichloro-5-cyano-pyrimidine as a yellow-brownish solid. For purification, the crude material was chromatographed on silica gel using a 5:1 mixture of cyclohexane and dichloromethane as the eluent giving 4.38 g (0.021 mol, 59% of theory) of 2,4,6-trichloro-5-cyano-pyrimidine as a white solid; MS: $[M]^+ = 207$.

b) 4-Chloro-2,6-bis-cyclopropylamino-pyrimidine-5-carbonitrile

To a solution of 500 mg (2.4 mmol) of 2,4,6-trichloro-5-cyano-pyrimidine in 30 ml of dioxane were added at room temperature 0.84 ml (4.8 mmol) of N-ethyl-diisopropylamine and 0.52 ml (7.2 mmol) of cyclopropylamine. The yellow reaction mixture was stirred at room temperature during 18 hours, then, for working-up, it was evaporated under reduced pressure. The residue obtained was then chromatographed on silica gel using a 3:1 mixture of dichloromethane and hexane as the eluent yielding 328 mg (1.3 mmol, 55% of theory) of 4-chloro-2,6-bis-cyclopropylamino-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 249$.

c) 2,4-Bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-cyclopropyl-amino-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine and N-ethyl-diisopropylamine in dioxane at 90 °C to yield 2,4-bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, light yellow solid; MS: $[M+H]^+ = 376$.

Example 39

2,4-Bis-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 4-Chloro-2,6-bis-(cyclopropylmethyl-amino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 38b, 2,4,6-trichloro-5-cyano-pyrimidine as prepared in example 38a was treated with aminomethyl-cyclopropane in ethanol at room temperature during 3 hours to yield the 4-chloro-2,6-bis-(cyclopropyl-methyl-amino)-pyrimidine-5-carbonitrile as a white solid; MS: $[M+H]^+ = 278$.

b) 2,4-Bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-(cyclopropyl-methyl-amino)-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in the presence of N-ethyl-diisopropylamine in dioxane at 80 °C during 18 hours to yield 2,4-bis-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 404$.

Example 40

4-(4-Phenyl-piperazin-1-yl)-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

a) 4-Chloro-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 38b, 2,4,6-trichloro-5-cyano-pyrimidine was treated with 2-(aminomethyl)-pyridine in dioxane at room temperature during 18 hours in the presence of N-ethyl-diisopropylamine to yield the 4-chloro-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 352$.

b) 4-(4-Phenyl-piperazin-1-yl)-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in the presence of N-ethyl-diisopropylamine in dioxane at 90 °C during 18 hours to yield 4-(4-phenyl-piperazin-1-yl)-2,6-bis-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, yellowish solid; MS: $[M+H]^+ = 478$.

Example 41

4-(Cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 4,6-Dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile and 2,4-dichloro-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

A solution of 3.0 g (14.4 mmol) of 2,4,6-trichloro-5-cyano-pyrimidine (example 38a) and 2.51 ml (14.4 mmol) of N-ethyl-diisopropylamine in 90 ml of dioxane was treated at room temperature with 0.88 ml (14.4 mmol) of ethanolamine and stirred during 18 hours. For the working-up, the yellow solution was evaporated and the residue dissolved in 300 ml dichloromethane. The organic phase was washed twice with 50 ml of water, and the two aqueous phases were re-extracted with 50 ml of dichloromethane. The combined organic phases were dried over sodium sulfate and evaporated under reduced pressure. For purification and separation of the two isomers, the crude material (3.2 g) was chromatographed (2x) on silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent giving 0.85 g (3.6 mmol, 25% of theory) of the 2,4-dichloro-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (less polar isomer); MS: $[M]^+ = 232$; 1.51 g (6.5 mmol, 45% of theory) of the 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (more polar isomer); MS: $[M]^+ = 232$; and 0.26 g (1.1 mmol, 8% of theory) of a mixture of the two isomers.

b) 4-Chloro-6-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 38b, 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with aminomethyl-cyclopropane in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-chloro-6-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 268$.

c) 4-(Cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-6-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 394$.

Example 42

4-(Cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-6-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41b) was treated with 4-phenyl-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield the 4-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid;
MS: $[M+H]^+ = 393$.

Example 43

4-(Cyclopropylmethyl-amino)-6-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-6-(cyclopropylmethyl-amino)-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41b) was treated with 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-(cyclopropylmethyl-amino)-6-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 409$.

Example 44

4-Cyclopropylamino-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

a) 4-Chloro-6-cyclopropylamino-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 38b, 4,6-dichloro-2-(2-hydroxy-ethyl-amino)-pyrimidine-5-carbonitrile was treated with cyclopropylamine in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-chloro-6-cyclopropylamino-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid;
MS: $[M+H]^+ = 254$.

b) 4-Cyclopropylamino-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, the 4-chloro-6-cyclopropylamino-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with the 4-(4-fluoro-phenyl)-piperidine hydrochloride in dioxane in the presence of N-ethyl-diisopropyl-amine at 90 °C to yield 4-cyclopropylamino-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 397$.

Example 45

4-Cyclopropylamino-6-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-6-cyclopropylamino-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 44a) was treated with 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-cyclopropylamino-6-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 395$.

Example 46

4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

a) 4-Chloro-2-(2-hydroxy-ethylamino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 38b, 4,6-dichloro-2-(2-hydroxy-ethyl-amino)-pyrimidine-5-carbonitrile was treated with 3-picolylamine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature to yield 4-chloro-2-(2-hydroxy-ethylamino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as a colorless foam.

b) 4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4-chloro-2-(2-hydroxy-ethyl-amino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile was treated with 4-

(4-fluorophenyl)-piperidine hydrochloride in dioxane in the presence of N-ethyl-diisopropyl-amine at 80 °C to yield the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethyl-amino)-6-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 448$.

Example 47

2-Cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 4-Chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

A solution of 0.5 g (2.0 mmol) of 4-chloro-6-(2-hydroxy-ethylamino)-2-methylsulfanyl-pyrimidine-5-carbonitrile (Timkevicius, S., *Chemija* 1997, 1, 58-61) in 30 ml of dichloromethane was treated at room temperature with 755 mg (70%, 3.0 mmol) of 3-chloro-perbenzoic acid and stirred during 18 hours. For the working-up, the reaction mixture was diluted with 20 ml of dichloromethane and washed rapidly with 50 ml of a cold, saturated aqueous solution of sodium hydrogencarbonate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure. To the obtained crude 4-chloro-6-(2-hydroxy-ethylamino)-2-methanesulfonyl-pyrimidine-5-carbonitrile were added 5 ml of dichloromethane, then 0.5 ml (3.0 mmol) of N-ethyl-diisopropylamine and 235 mg (4.0 mmol) of cyclopropylamine. The mixture was stirred at room temperature during 18 hours, then it was evaporated under reduced pressure and the residue obtained directly chromatographed on silica gel using a 3:1 mixture of dichloromethane and ethyl acetate as the eluent yielding 340 mg (1.34 mmol, 65% of theory) of the 4-chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 254$.

b) 2-Cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

A mixture of 70 mg (0.27 mmol) of 4-chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile and 0.047 ml (0.27 mmol) of N-ethyl-diisopropylamine in 5 ml of dioxane was treated with 49 mg (0.3 mg) of 1-phenyl-piperazine. The solution was heated to 100 °C during 18 hours, thereafter, for the working-up, evaporated under reduced pressure. For purification, the residue obtained was chromatographed by preparative HPLC on RP18-silica gel using a gradient of a mixture of acetonitrile and water (plus 0.1% of formic acid) as the eluent to give 60 mg (0.16 mmol, 58% of theory) of the 2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-

phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as a white powder after lyophilization; MS: $[M+H]^+ = 380$.

Example 48

2-(Cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 4-Chloro-2-(cyclopropylmethyl-amino)-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47a, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-methanesulfonyl-pyrimidine-5-carbonitrile was treated with amino-methyl-cyclopropane in dioxane in the presence of N-ethyl-diisopropylamine at 40 °C to yield 4-chloro-2-(cyclopropylmethyl-amino)-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 268$.

b) 2-(Cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, 4-chloro-2-(cyclopropylmethyl-amino)-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield 2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 394$.

Example 49

4-(2-Hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

a) 4-Chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47a, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-methanesulfonyl-pyrimidine-5-carbonitrile was treated with 3-picolyl-amine in dioxane in the presence of N-ethyl-diisopropylamine at 40 °C to yield 4-chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as a brown solid which was used in the next step without further purification and characterization.

b) 4-(2-Hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield 4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+$ = 431.

Example 50

2-(Cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, 4-chloro-2-(cyclopropylmethyl-amino)-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 48a) was treated with the 1-(4-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropyl-amine at 100 °C to yield 2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+$ = 412.

Example 51

2-Cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, 4-chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 47a) was treated with the 1-(4-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield the 2-cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+$ = 398.

Example 52

4-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile (example 49a) was treated with 1-(4-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at 90 °C to yield 4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, light brown powder; MS: $[M+H]^+ = 449$.

Example 53

2-(Cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

a) 4-(2-Hydroxy-ethylamino)-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

A solution of 0.47 g (1.9 mmol) of 4-chloro-6-(2-hydroxy-ethylamino)-2-methylsulfanyl-pyrimidine-5-carbonitrile (Timkevicius, S., *Chemija* 1997, 1, 58-61) and 0.33 ml (1.9 mmol) of N-ethyl-diisopropylamine in 5 ml of dichloromethane was treated at 30 °C with 310 mg (1.9 mmol) of 4-phenyl-piperidine and stirred during 7 hours. For the working-up, the reaction mixture was evaporated under reduced pressure, and the residue obtained was directly chromatographed on silica gel using a 99:1 mixture of dichloromethane and methanol as the eluent yielding 490 mg (1.33 mmol, 70% of theory) of the 4-(2-hydroxy-ethylamino)-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 370$.

b) 2-(Cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

A solution of 0.1 g (0.26 mmol) of 4-(2-hydroxy-ethylamino)-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile in 3 ml of dichloromethane was treated at 0 °C with 95 mg (0.39 mmol) of 3-chloro-perbenzoic acid, and, thereupon, stirred at room temperature during 3 hours. For the working-up, the reaction mixture was diluted with 5 ml of dichloromethane and washed rapidly with 5 ml of a cold, saturated aqueous solution of sodium hydrogencarbonate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure. To the obtained crude 4-(2-

hydroxy-ethylamino)-2-methanesulfonyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile were added 5 ml of dichloromethane and 0.045 ml (0.5 mmol) of aminomethyl-cyclopropane. The mixture was stirred at 40 °C during 18 hours, then it was evaporated under reduced pressure and the residue obtained directly chromatographed by preparative HPLC on RP18-silica gel using a gradient of a mixture of acetonitrile and water (plus 0.1% of formic acid) as the eluent to give 35 mg (0.89 mmol, 35% of theory), of the 2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M]^+ = 392$.

Example 54

4-(2-Hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile (example 49a) was treated with 4-phenyl-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield 4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, brownish powder; MS: $[M+H]^+ = 430$.

Example 55

2-Cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, 4-chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 47a) was treated with 4-phenyl-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield 2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 379$.

Example 56

4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, the crude 4-chloro-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile (example 49a) was treated with the 4-(4-fluorophenyl)-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile as an amorphous, light brown; MS: $[M+H]^+ = 448$.

Example 57

2-(Cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

a) 4-Chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-pyrimidine-5-carbonitrile

A dispersion of 0.5 g (2.3 mmol) of 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (*J. Heterocycl. Chem.* 1971, 8, 445-453) and 0.65 g (5.0 mmol) of N-ethyl-diisopropylamine in 40 ml of dioxane was treated at room temperature with 0.54 g (5.0 mmol) of 4-(4-fluorophenyl)-piperidine hydrochloride during 18 h. For the working-up, the reaction mixture was evaporated, and, thereafter, the residue obtained was directly chromatographed on silica gel using toluene as the eluent yielding 660 mg (1.8 mmol, 80% of theory) of 4-chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 363$.

b) 4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-2-methylsulfanyl-pyrimidine-5-carbonitrile

A dispersion of 200 mg (0.55 mmol) of 4-chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-pyrimidine-5-carbonitrile and 84 mg (0.6 mmol) of N-ethyl-diisopropylamine in 4 ml of dioxane was treated at 65 °C with 37 mg (0.6 mmol) of ethanolamine during 18 h. For the working-up, the reaction mixture was evaporated, and, thereafter, the residue obtained was directly chromatographed on silica gel using a 5:1 mixture of toluene and ethyl acetate as the eluent yielding 177 mg (0.46 mmol, 83% of theory) of the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-2-

methylsulfanyl-pyrimidine-5-carbonitrile as a yellowish oil which crystallized on standing. MS: $[M+H]^+ = 388$.

c) 2-(Cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

A solution of 150 mg (0.4 mmol) of 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-2-methylsulfanyl-pyrimidine-5-carbonitrile in 8 ml of dichloromethane was cooled to 0 °C and treated with a solution of 172 mg (70%, 0.7 mmol) of 3-chloro-perbenzoic acid. The reaction mixture was warmed to room temperature and stirring was continued during 4 hours (completion of the reaction was checked by TLC). For the working-up, the reaction mixture was diluted with 20 ml of dichloromethane and washed rapidly with 10 ml of a cold, saturated aqueous solution of sodium hydrogencarbonate. The organic phase was separated, dried over sodium sulfate., and evaporated under reduced pressure. Thereupon, without further working-up, the residue obtained was dissolved in 15 ml of dioxane and the solution was treated with 39 mg (0.52 mmol) of aminomethyl-cyclopropane. After 18 hours at 40 °C, the solution was evaporated and the residue obtained was then directly chromatographed by preparative HPLC on RP18-silica gel using a gradient of a mixture of acetonitrile and water (plus 0.1% of formic acid) as the eluent to give 48 mg (0.12 mmol, 25% of theory) of the 2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as a white solid; MS: $[M+H]^+ = 411$.

Example 58

2-Cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 47b, 4-chloro-2-cyclopropylamino-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 47a) was treated with the 4-(4-fluorophenyl)-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at 100 °C to yield the 2-cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 397$.

Example 59

4-(4-Phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

a) 4-Chloro-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 57a, the 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (*J. Heterocycl. Chem.* 1971, 8, 445-453) was treated with 4-phenyl-piperidine in the presence of N-ethyl-diisopropylamine at room temperature during 18 hours to yield the 4-chloro-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 345$.

b) 2-Methylsulfanyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

A solution of 56 mg (0.55 mmol) of 2,2,2-trifluoroethanol in 5 ml of tetrahydrofurane was cooled to 0 °C and treated under an argon atmosphere with 23 mg (0.52 mmol) of sodium hydride (55% dispersion in oil). The mixture was kept at 0 °C during 10 min, then a solution of 200 mg (0.58 mmol) of 4-chloro-2-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile in 5 ml of tetrahydrofurane was added and, thereupon, the mixture was warmed to room temperature and stirring continued during 36 hours. For the working-up, the reaction mixture was evaporated and the residue obtained was directly chromatographed on silica gel using a 9:1 mixture of hexane and ethyl acetate as the eluent yielding 142 mg (0.35 mmol, 60% of theory) of the 2-methylsulfanyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 409$.

c) 4-(4-Phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 57c, the 2-methylsulfanyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile was oxidized by 3-chloro-perbenzoic acid to the 2-methanesulfonyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile which was then treated in crude form with 3-picolylamine in dioxane at 40 °C during 18 hours to yield the 4-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 469$.

Example 60

2-(2-Hydroxy-ethylamino)-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 57c, 2-methylsulfanyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile was oxidized by 3-chloro-perbenzoic acid to 2-methanesulfonyl-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile which was then treated in crude form with ethanolamine in dioxane at 40 °C during 18 hours to yield the 2-(2-hydroxy-ethylamino)-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 422$.

Example 61

4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

a) 4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 59b, 4-chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-pyrimidine-5-carbonitrile (example 57a) was treated with 2,2,2-trifluoroethanolate in tetrahydrofurane at room temperature during 18 hours to yield the 4-phenyl-piperidine in the presence of N-ethyl-diisopropylamine at room temperature during 18 hours to yield 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as an amorphous, yellow solid; MS: $[M+H]^+ = 427$.

b) 4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 57c, the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile was oxidized by 3-chloro-perbenzoic acid to 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methanesulfonyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile which was then treated with 3-picolylamine in dioxane at 40 °C during 18 hours to yield the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as an amorphous, light brown solid; MS: $[M+H]^+ = 487$.

Example 62

4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 57c, 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methylsulfanyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile (example 61a) was oxidized by 3-chloro-perbenzoic acid to the 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methanesulfonyl-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile which was then treated with ethanolamine in dioxane at 40 °C during 4 hours to yield 4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile as a clorless oil; MS: $[M+H]^+ = 440$.

Example 63

4-Chloro-2-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

a) 4,6-Dichloro-2-(cyclopropylmethyl-amino)-pyrimidine-5-carbonitrile

A solution of 1.0 g (5.4 mmol) of 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (*J. Heterocycl. Chem.* 1971, 8, 445-453) in 30 ml of dichloromethane was cooled to 0 °C and treated with 1.59 g (70%, 6.4 mmol) of 3-chloro-perbenzoic acid. The reaction mixture was warmed to room temperature and stirring was continued during 3 hours (completion of the reaction was checked by TLC). For the working-up, the reaction mixture was diluted with 70 ml of dichloromethane and washed rapidly with 30 ml of a cold, saturated aqueous solution of sodium hydrogencarbonate. The organic phase was separated and dried over sodium sulfate. Thereupon, without further working-up, the solution was treated with 385 mg (5.4 mmol) of aminomethyl-cyclopropane. After 18 hours at room temperature, the solution was evaporated and the residue obtained was then chromatographed on silica gel using a 10:1 mixture of hexane and ethyl acetate as the eluent giving 450 mg (1.85 mmol, 34% of theory) of the 4,6-dichloro-2-(cyclopropyl-methyl-amino)-pyrimidine-5-carbonitrile as a white powder; MS: $[M]^+ = 243$.

b) 4-Chloro-2-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(cyclopropyl-methyl-amino)-pyrimidine-5-carbonitrile was treated with 1-phenyl-piperazine in the

presence of N-ethyl-diisopropylamine in dioxane at room temperature during 18 hours to yield 4-chloro-2-(cyclopropylmethyl-amino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 369$.

Example 64

4-Chloro-2-(cyclopropylmethyl-amino)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(cyclopropyl-methyl-amino)-pyrimidine-5-carbonitrile (example 63a) was treated with 1-(4-fluoro-phenyl)-piperazine in the presence of N-ethyl-diisopropylamine in dioxane at 90 °C to yield 4-chloro-2-(cyclopropylmethyl-amino)-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 387$.

Example 65

4-Chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41a) was treated with 1-phenyl-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature to yield 4-chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 359$.

Example 66

4-Chloro-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41a) was treated with 4-(4-fluoro-phenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature to yield 4-chloro-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 377$.

Example 67

4-Chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41a) was treated with 4-phenyl-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature to yield 4-chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 358$.

Example 68

4-Chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 4,6-dichloro-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile (example 41a) was treated with 4-(4-fluoro-phenyl)-piperidine hydrochloride in dioxane in the presence of N-ethyl-diisopropyl-amine at room temperature to yield 4-chloro-6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile as a white lyophilisate; MS: $[M+H]^+ = 376$.

Example 69

2-Amino-4-methylsulfanyl-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, the 2-amino-4-bromo-6-methylsulfanyl-pyrimidine-5-carbonitrile, which was prepared from 2,2-dicyano-1-methylsulfanyl-vinyl-cyanamide sodium salt as described in European Patent Application EP 244 360 A2 (1987) with excess hydrogen bromide in acetic acid between 0 °C and room temperature, was treated with 1-phenyl-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield the 2-amino-4-methyl-sulfanyl-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 327$.

Example 70

2-Amino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 2-amino-4-bromo-6-methylsulfanyl-pyrimidine-5-carbonitrile (see example 69) was treated with 1-(4-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield 2-amino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile as a yellow powder; MS: $[M+H]^+ = 345$.

Example 71

2-Amino-4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 2-amino-4-bromo-6-methylsulfanyl-pyrimidine-5-carbonitrile (see example 69) was treated with the 1-(2-fluorophenyl)-piperazine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield the 2-amino-4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 345$.

Example 72

2-Amino-4-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 2-amino-4-bromo-6-methylsulfanyl-pyrimidine-5-carbonitrile (see example 69) was treated with 4-phenyl-piperidine in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield 2-amino-4-methylsulfanyl-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile as a yellow foam; MS: $[M+H]^+ = 326$.

Example 73

2-Amino-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, the 2-amino-4-bromo-6-methylsulfanyl-pyrimidine-5-carbonitrile (see example 69) was treated with the 4-(4-fluorophenyl)-piperidine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield 2-amino-4-[4-(4-fluoro-

phenyl)-piperidin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 344$.

Example 74

2-Amino-4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile

In analogy to the procedure described in example 20b, 2-amino-4-bromo-6-methyl-sulfanyl-pyrimidine-5-carbonitrile (see example 69) was treated with 4-(4-fluorophenyl)-1,2.3,6-tetrahydro-pyridine hydrochloride in dioxane in the presence of N-ethyl-diisopropylamine at room temperature during 36 hours to yield 2-amino-4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-6-methylsulfanyl-pyrimidine-5-carbonitrile as a yellow solid; MS: $[M+H]^+ = 342$.

Example 75

5'-Ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

and

6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

a) 5-Ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide

A solution of 8.32 g (80.61 mmol) 2-amino-malonic acid diamide and 9.75 g (83.26 mmol) of 2,3-pentanedione in 60 ml of water was heated under reflux for 18 hours. After cooling to room temperature the crystals formed were collected by filtration and dried in vacuo. There were thus obtained 9.52 g (52.54 mmol, 65.2% of theory) of a 3:2 or a 2:3 mixture of the 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and the
5-ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide as yellow solid; MS: 181 $(M)^+$.

b) 3-Chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile (1:1 mixture of the two isomers)

1.81 g (10.0 mmol) of the 3:2 or 2:3 mixture of the 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and the 5-ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide were suspended in 4.2 ml (30 mmol) of triethylamine. Then, 30 ml of phosphorus oxychloride were slowly added between 0 °C and 5 °C and the

reaction mixture heated under reflux for 3 hours. It was then cooled to 20 °C, 5.3 g (25 mmol) of phosphorus pentachloride were added and the reaction mixture heated again under reflux for 3 hours. It was then added to water while maintaining a temperature of 20 °C to 25 °C. The aqueous phase was subsequently extracted 5 times with 100 ml of ether and the combined ether phases washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel using a 1:1 v/v mixture of dichloromethane and hexane as eluent giving 1.0 g (5.5 mmol, 55% of theory) of a 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile in form of an orange red oil; MS: 181 $(M)^+$.

c) 5'-Ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile and 6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

0.416 mg (3.0 mmol) of potassium carbonate were added to a solution of 0.182 g (1.0 mmol) of the 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile and of 0.199 g (1.2 mmol) of 1-phenylpiperazine in 10.0 ml of N,N-dimethylformamide and the reaction mixture was stirred at room temperature for 16 hours. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 4:1 to 0:100 v/v gradient of hexane and dichloromethane as the eluent giving 0.067 g (0.218 mmol, 21.8 % of theory) of the 5'-ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as orange oil; MS: 308 $(M+H)^+$; and 0.043 g (0.14 mmol, 14 % of theory) of the 6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as yellow solid; m.p. 99-101 °C; MS: 308 $(M+H)^+$.

Example 76

5'-Ethyl-4-(4-fluoro-phenyl)-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

and

6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

In analogy to the procedure as described in example 75c, the 1:1 mixture of 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-pyrazine-2-

carbonitrile was reacted with 1-(4-fluorophenyl)piperazine and N-ethyldiisopropylamine in N,N-dimethylformamide at room temperature for 16 hours to give a 1:1 mixture of 5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile and 6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as a light yellow oil; MS: 326 $(M+H)^+$.

Example 77

6-Ethyl-5-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile

and

5-ethyl-6-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile

In analogy to the procedure as described in example 75c, the 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile was reacted with 4-phenylpiperidine and N-ethyldiisopropylamine in N,N-dimethylformamide at room temperature for 16 hours to give a 1:1 mixture of 6-ethyl-5-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile and 5-ethyl-6-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile as a light yellow oil; MS: 307 $(M+H)^+$.

Example 78

6-Ethyl-5-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile

and

5-ethyl-6-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile

In analogy to the procedure as described in example 75c, the 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile was reacted with 1,2,3,6-tetrahydro-4-phenylpiperidine hydrochloride and N-ethyldiisopropylamine in N,N-dimethylformamide at room temperature for 16 hours to give a 1:1 mixture of 6-ethyl-5-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile and 5-ethyl-6-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile as a light brown oil; MS: 305 $(M+H)^+$.

Example 79

5'-Ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

and

6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

a) 3-Chloro-6-ethyl-5-methyl-1-oxy-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-1-oxy-pyrazine-2-carbonitrile

0.212 g (2.18 mmol) of hydrogen peroxide (35% solution in water) were slowly added to a solution of 0.193 g (1.06 mmol) of the 1:1 mixture of 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile (example 75b) in 5.0 ml trifluoroacetic acid. The reaction mixture was then stirred at room temperature for 5 hours. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 9:1 to 1:1 v/v gradient of hexane and ethylacetate as the eluent giving 0.178 g (0.09 mmol, 85 % of theory) of the 1:1 mixture of 3-chloro-6-ethyl-5-methyl-1-oxy-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-1-oxy-pyrazine-2-carbonitrile as light yellow oil; MS: 197 $(M)^+$.

b) 5'-Ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile and 6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

A solution of 0.416 g (2.10 mmol) of the 1:1 mixture of 3-chloro-6-ethyl-5-methyl-1-oxy-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-1-oxy-pyrazine-2-carbonitrile, of 0.465 g (2.53 mmol) of 1-(4-fluorophenyl)piperazine and of 0.833 g (6.31 mmol) of N-ethyldiisopropylamine in 15.0 ml of N,N-dimethylformamide was strirred at room temperature for 18 hours. The reaction mixture was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 95:5 to 0:100 v/v gradient of hexane and dichloromethane as eluent giving 0.361 g (1.06 mmol, 50.3 % of theory) of a mixture of 5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile and 6'-ethyl-4-(4-fluoro-phenyl)-

5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile [1:1], 100 mg of which was further separated by prep. HPLC (Microsorb 80-120-5C Si) using a 99:1 v/v mixture of n-heptane and ethanol as eluent to give 0.030 g of the 5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as a light brown amorphous solid; MS: 342 $(M+H)^+$ and 0.024 g of the 6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as a light brown amorphous solid; MS: 342 $(M+H)^+$.

Example 80

4-(4-Fluoro-phenyl)-6'-methyl-5'-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

In analogy to the procedure described in example 75a-c, 1-phenyl-1,2-propanedione and 2-aminomalonamide were heated in an aqueous solution to give 5-methyl-3-oxo-6-phenyl-3,4-dihydro-pyrazine-2-carboxylic acid amide. Then, the 5-methyl-3-oxo-6-phenyl-3,4-dihydro-pyrazine-2-carboxylic acid amide was treated with triethylamine and phosphorus pentachloride in phosphorus oxychloride at reflux to give 3-chloro-5-methyl-6-phenyl-pyrazine-2-carbonitrile. The 3-chloro-5-methyl-6-phenyl-pyrazine-2-carbonitrile was finally treated with 1-(4-fluorophenyl)piperazine and N-ethyldiisopropyl-amine in N,N-dimethylformamide at room temperature to yield the 4-(4-fluoro-phenyl)-6'-methyl-5'-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as yellow solid; m.p. 117-120 °C; MS: 374 $(M+H)^+$.

Example 81

3-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-5-methyl-6-phenyl-pyrazine-2-carbonitrile

In analogy to the procedure described in example 75c, the 3-chloro-5-methyl-6-phenyl-pyrazine-2-carbonitrile was treated with 4-(4-fluoro-phenyl)-piperidine and N-ethyldiisopropylamine in N,N-dimethylformamide at room temperature to yield the 3-[4-(4-fluoro-phenyl)-piperidin-1-yl]-5-methyl-6-phenyl-pyrazine-2-carbonitrile as yellow oil; MS: 373 $(M+H)^+$.

Example 82

3-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile

a) 3-Bromo-5-chloro-pyrazine-2-carbonitrile

A solution of 0.309 g (2.00 mmol) of 3-amino-5-chloro-pyrazine-2-carbonitrile (*J.Org.Chem.* 1975, 40, 2341-2347) in 5.0 ml of acetonitrile was slowly added at a temperature of 65 °C to a suspension of 0.903 g (4.0 mmol) of copper(II)bromide and 0.344 g (3.0 mmol) of tert.-butyl nitrite in 20.0 ml of acetonitrile. The reaction mixture was stirred at 65 °C for 1 hour, then cooled to room temperature. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 4:1 to 0:10 v/v gradient of hexane and dichloromethane as the eluent giving 0.333 g (1.53 mmol, 76.2 % of theory) of the 3-bromo-5-chloro-pyrazine-2-carbonitrile as light yellow solid; m.p. 66-67 °C; MS: 218 $(M)^+$.

b) 3-Bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile

0.061 g (1.00 mmol) of ethanolamine were added slowly at room temperature to a solution of 0.218 g (1.0 mmol) of the 3-bromo-5-chloro-pyrazine-2-carbonitrile and 0.264 g (2.0 mmol) of N-ethyldiisopropylamine in 15.0 ml of dioxane. The reaction mixture was stirred at room temperature for 18 hours. It was subsequently poured into 50 ml of an ice/water/sodium hydrogen carbonate mixture and extracted 3 times with 50 ml of ethylacetate. The combined ethylacetate phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 100:0 to 95:5 v/v gradient of dichloromethane and methanol as the eluent giving 0.131 g (0.539 mmol, 53.9 % of theory) of the 3-bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile as yellow solid; m.p. 158-160 °C; MS: 243 $(M)^+$.

c) 3-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile

0.415 g (3.00 mmol) of potassium carbonate were added slowly at room temperature to a solution of 0.243 g (1.0 mmol) of the 3-bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile and 0.324 g (1.5 mmol) of the 4-(4-fluoro-phenyl)-piperidine hydrochloride in 15.0 ml of N,N-dimethylformamide. The reaction mixture was stirred at room

temperature for 64 hours and at 80 °C for 5 hours. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was recrystallized from hexane/ethylacetate giving 0.314 g (0.92 mmol, 92% of theory) of the 3-[4-(4-fluoro-phenyl)-piperidin-1-yl]-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile as yellow solid; m.p. 155-158 °C; MS: 342 $(M+H)^+$.

Example 83

4-(4-Fluoro-phenyl)-6'-(2-hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile

In analogy to the procedure described in example 82c, 3-bromo-5-(2-hydroxy-ethyl-amino)-pyrazine-2-carbonitrile was treated with 1-(4-fluorophenyl)piperazine in the presence of potassium carbonate in N,N-dimethylformamide between room temperature and 80 °C to yield 4-(4-fluoro-phenyl)-6'-(2-hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile as light yellow solid; m.p. 149-151 °C; MS: 343 $(M+H)^+$.

Example 84

3-(2-Hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile

a) 5-Chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile

A solution of 500 mg (2.7 mmol) of 3-methylsulfanyl-5-oxo-4,5-dihydro-[1,2,4]triazine-6-carboxylic acid amide (J.J.Huang, *J.Org.Chem.* 1985, 50, 2293-2298; H.Wang et al., *Hua Hsueh Hsueh Pao* 1964, 30 (2), 183-192; CA Vol. 61, 8311b) in 38 ml (408 mmol) of phosphorus oxychloride was heated to reflux during 1.5 h. After cooling the dark brown reaction mixture, the excess of phosphorus oxychloride was evaporated under reduced pressure. To destroy residues of phosphorus oxychloride and to neutralize the reaction mixture, the resulting red-brown oily residue was dissolved in 15 ml of toluene and the solution added to an ice-cold saturated aqueous solution of sodium hydrogencarbonate. The organic phase was diluted with 100 ml of dichloromethane, separated from the aqueous phase, dried over sodium sulfate, and evaporated under reduced pressure. The resulting 5-chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile was obtained as a brown oil and was used in the following reactions without further purification.

b) 3-Methylsulfanyl-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile

A solution of 130 mg (0.66 mmol) of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride in 5 ml of dioxane was treated at room temperature with 0.23 ml (1.32 mmol) of N-ethyl-diisopropylamine and, thereupon, with 112 mg (0.60 mmol) of crude 5-chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile. The reaction mixture was stirred at 50 °C during 18 hours. For the working-up, the solution was evaporated under reduced pressure and the residue was chromatographed on silica gel with a 2:1 mixture of hexane and ethylacetate as the eluent. There were obtained 120 mg (0.34 mmol, 64.5% of theory) of 3-methylsulfanyl-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile in the form of an orange powder; MS: $[M+H]^+ = 310$.

c) 3-(2-Hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile

A mixture of 68 mg (0.21 mmol) of 3-methylsulfanyl-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile and 14.5 mg (0.23 mmol) ethanolamine in 1 ml of dioxane was stirred at 120 °C overnight. For the working-up, the solution was evaporated under reduced pressure and the residue was chromatographed on silica gel with a 90:10:0.1 mixture of dichloromethane, methanol, and ammonium hydroxide as the eluent. There were obtained 35 mg (0.10 mmol, 50% of theory) of 3-(2-hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile as an amorphous, white solid; MS : 323 $(M+H)^+$;

Example 85

3-(2-Hydroxy-ethylamino)-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile

a) 3-Methylsulfanyl-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile

In analogy to the procedure described in example 84b, the crude 5-chloro-3-methyl-sulfanyl-[1,2,4]triazine-6-carbonitrile (see example 84a) was treated with 1-phenyl-piperazine in ethanol in the presence of N-ethyl-diisopropylamine at room temperature during 3 days to yield 3-methylsulfanyl-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile as a white solid; MS: $[M+H]^+ = 313$.

b) 3-(2-Hydroxy-ethylamino)-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile

In analogy to the procedure described in example 84c, 3-methylsulfanyl-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile was treated with ethanolamine in a sealed tube at 140 °C during 18 hours to yield 3-(2-hydroxy-ethylamino)-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile as an amorphous, white solid; MS: $[M+H]^+ = 326$.

Example 86

{2-[6-Cyano-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester

In analogy to the procedure described in example 84c, 3-methylsulfanyl-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazine-6-carbonitrile was treated with N-Boc-ethylene-diamine in a sealed tube at 130°C during 48 hours to yield {2-[6-cyano-5-(4-phenyl-piperazin-1-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester as an amorphous, light yellow solid; MS: $[M+H]^+ = 425$.

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

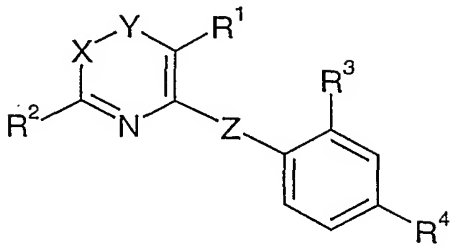
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

Claims

1. Compounds of the general formula



I

wherein

R^1 signifies nitro or cyano;

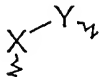
R^2 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl or $-NHR^{10}$; and

R^{10} signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $-(CH_2)_m\text{-}OR^{11}$, $-(CH_2)_p\text{-}(C_3\text{-}C_6)$-cycloalkyl, $-(CH_2)_m\text{-}NH\text{-}C(O)O\text{-}(C_1\text{-}C_7)$-alkyl or $-(CH_2)_p$-pyridyl; and

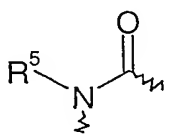
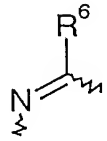
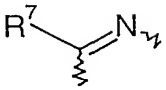
R^{11} signifies hydrogen or $(C_1\text{-}C_7)$-alkyl;

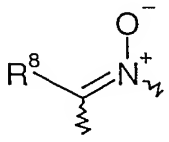
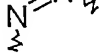
R^3 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, fluoro, hydroxy, $(C_1\text{-}C_7)$-alkoxy, $(C_1\text{-}C_7)$-alkylthio, cyano or nitro;

R^4 signifies hydrogen or fluoro;



signifies

(a)  (b)  (c) 

(d)  or (e)  , wherein

R^5 signifies hydrogen, $(C_1\text{-}C_7)$-alkyl, $(C_1\text{-}C_7)$-alkenyl, $-(CH_2)_m\text{-}OR^{11}$, fluoro-$(C_1\text{-}C_7)$-alkyl or $-(CH_2)_n\text{-}CN$;

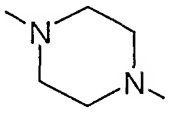
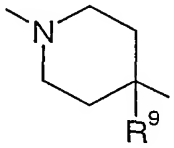
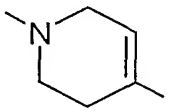
R^6 signifies (C_1-C_7)-alkyl, halogen, hydroxy, (C_1-C_7)-alkoxy, (C_1-C_7)-alkylthio, -O-$(CH_2)_m$-OR^{11}, -O-fluoro-(C_1-C_7)-alkyl or –NHR^{12}; and

R^{12} signifies (C_1-C_7)-alkyl, -$(CH_2)_m$-OR^{11}, -$(CH_2)_p$-(C_3-C_6)-cycloalkyl or -$(CH_2)_p$-pyridyl;

R^7 signifies hydrogen, (C_1-C_7)-alkyl or phenyl;

R^8 signifies hydrogen, (C_1-C_7)-alkyl or phenyl;

Z signifies

(i)  (ii)  (iii) 

, wherein

R^9 signifies hydrogen, hydroxy or cyano;

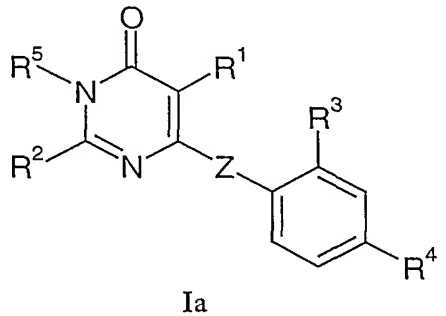
m is independently from each other in each occurence 2, 3, 4, 5 or 6;

n is independently from each other in each occurence 1, 2, 3, 4, 5 or 6; and

p is independently from each other in each occurence 0, 1, 2, 3, 4, 5 or 6;

as well as their pharmaceutically acceptable salts.

2. Compounds in accordance with claim 1 of the general formula



Ia

wherein R^1 to R^5 and Z have the significances as defined in claim1,

as well as their pharmaceutically acceptable salts.

3. Compounds of formula Ia in accordance with claim 2, wherein

R^1, R^4 and R^5 have the significances as defined in claim 1;

R^2 signifies (C_1-C_7)-alkyl or –NHR^{10};

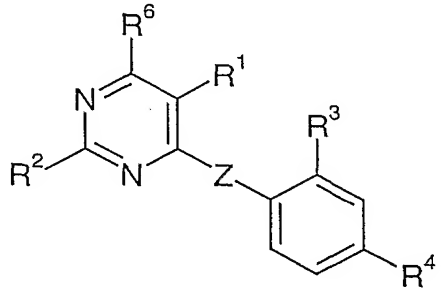
R^3 signifies hydrogen or fluoro; and

Z has the significances as defined in claim 1, wherein R^9 is hydrogen.

4. Compounds of formula Ia in accordance with claim 3, wherein R^3 is hydrogen and R^5 signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$ or fluoro-(C_1-C_7)-alkyl.

5. Compounds of formula Ia in accordance with claim 4, which are selected from the group consisting of
6-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-methyl-5-nitro-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
2-methyl-5-nitro-6-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-3-(2-hydroxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one,
6-[4-(4-fluoro-phenyl)-piperidin-1-yl]-3-(2-methoxy-ethyl)-2-methyl-5-nitro-3H-pyrimidin-4-one, or
3-ethyl-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-3H-pyrimidin-4-one.

6. Compounds in accordance with claim 1 of the general formula



Ib

wherein R^1 to R^4, R^6 and Z have the significances as defined in claim1,
as well as their pharmaceutically acceptable salts.

7. Compounds of formula Ib in accordance with claim 6, wherein
R^1 and R^4 have the significances as defined in claim 1;
R^2 signifies (C_1-C_7)-alkyl or $-NHR^{10}$; and
R^{10} signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR^{11}$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl;

R^3 signifies hydrogen or fluoro;

Z has the significances as defined in claim 1, wherein R^9 is hydrogen;

R^6 signifies halogen, (C_1-C_7)-alkoxy, (C_1-C_7)-alkylthio, $-O-(CH_2)_m-OR^{11}$, -O-fluoro-(C_1-C_7)-alkyl or $-NHR^{12}$; and

R^{12} signifies (C_1-C_7)-alkyl, $-(CH_2)_m-OR$ or $-(CH_2)_p-(C_3-C_6)$-cycloalkyl.

8. Compounds of formula Ib in accordance with claim 7, wherein

R^2 signifies (C_1-C_7)-alkyl or $-NHR^{10}$;

R^{10} signifies $-(CH_2)_m-OH$, $-(CH_2)_p-(C_3-C_6)$-cycloalkyl, $-(CH_2)_m-NH-C(O)O-(C_1-C_7)$-alkyl or $-(CH_2)_p$-pyridyl;

R^3 signifies hydrogen;

R^6 signifies halogen, (C_1-C_7)-alkylthio, $-O-(CH_2)_m-OR^{11}$, -O-fluoro-(C_1-C_7)-alkyl or $-NHR^{12}$; and

R^{12} signifies $-(CH_2)_m-OR^{11}$ or $-(CH_2)_p-(C_3-C_6)$-cycloalkyl.

9. Compounds of formula Ib in accordance with claim 8, which are selected from the group consisting of

2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,

4-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,

4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-[(pyridin-3-ylmethyl)-amino]-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,

2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,

2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,

4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-(2-hydroxy-ethylamino)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,

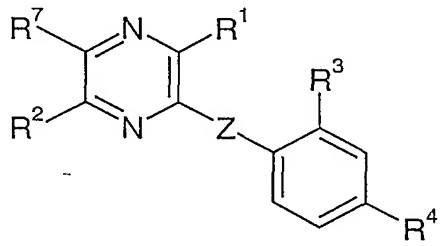
2-(cyclopropylmethyl-amino)-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile,

2-(cyclopropylmethyl-amino)-4-[4-(4-fluoro-phenyl)-piperidin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,

4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-2-[(pyridin-3-ylmethyl)-amino]-pyrimidine-5-carbonitrile,

2-cyclopropylamino-4-[4-(4-fluoro-phenyl)-piperazin-1-yl]-6-(2-hydroxy-ethylamino)-pyrimidine-5-carbonitrile,
2-cyclopropylamino-4-(2-hydroxy-ethylamino)-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile,
2-(2-hydroxy-ethylamino)-4-(4-phenyl-piperidin-1-yl)-6-(2,2,2-trifluoro-ethoxy)-pyrimidine-5-carbonitrile,
4-chloro-2-(2-hydroxy-ethylamino)-6-(4-phenyl-piperidin-1-yl)-pyrimidine-5-carbonitrile,
2-{6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-2-methyl-5-nitro-pyrimidin-4-yloxy}-ethanol,
or
2,4-bis-cyclopropylamino-6-(4-phenyl-piperazin-1-yl)-pyrimidine-5-carbonitrile.

10. Compounds in accordance with claim 1 of the general formula



Ic

wherein R^1 to R^4, R^7 and Z have the significances as defined in claim 1,
as well as their pharmaceutically acceptable salts.

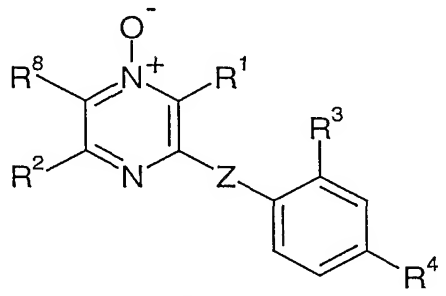
11. Compounds of formula Ic in accordance with claim 10, wherein
R^1 and R^4 have the significances as defined in claim 1;
R^2 signifies (C_1-C_7)-alkyl or –NHR^{10};
R^3 signifies hydrogen or fluoro;
Z has the significances as defined in claim 1, wherein R^9 is hydrogen; and
R^7 signifies (C_1-C_7)-alkyl or phenyl.

12. Compounds of formula Ic in accordance with claim 11, wherein R^2 signifies (C_1-C_7)-alkyl and R^3 signifies hydrogen.

13. Compounds of formula Ic in accordance with claim 12, which are selected from the group consisting of
4-(4-fluoro-phenyl)-6'-methyl-5'-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-

carbonitrile,
5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile,
6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile,
6-ethyl-5-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile,
5-ethyl-6-methyl-3-(4-phenyl-piperidin-1-yl)-pyrazine-2-carbonitrile,
6-ethyl-5-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile,
5-ethyl-6-methyl-3-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-pyrazine-2-carbonitrile,
5'-ethyl-6'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile, or
6'-ethyl-5'-methyl-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile.

14. Compounds in accordance with claim 1 of the general formula



Id

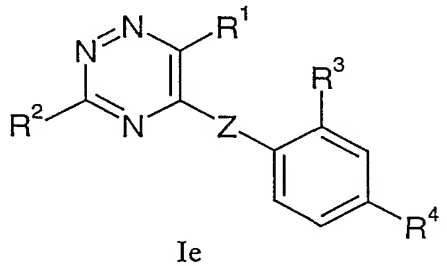
wherein R^1 to R^4, R^8 and Z have the significances as defined in claim 1,
as well as their pharmaceutically acceptable salts.

15. Compounds of formula Id in accordance with claim 14, wherein
R^1 and R^4 have the significances as defined in claim 1;
R^2 signifies (C_1-C_7)-alkyl;
R^3 signifies hydrogen or fluoro;
Z has the significances as defined in claim 1, wherein R^9 is hydrogen; and
R^8 signifies (C_1-C_7)-alkyl.

16. Compounds of formula Id in accordance with claim 15, which are selected from the group consisting of
5'-ethyl-4-(4-fluoro-phenyl)-6'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile, or

6'-ethyl-4-(4-fluoro-phenyl)-5'-methyl-4'-oxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-3'-carbonitrile.

17. Compounds in accordance with claim 1 of the general formula



Ie

wherein R^1 to R^4 and Z have the significances as defined in claim 1,

as well as their pharmaceutically acceptable salts.

18. Compounds of formula Ie in accordance with claim 17, wherein

R^1 and R^4 have the significances as defined in claim 1;

R^2 signifies $-NHR^{10}$;

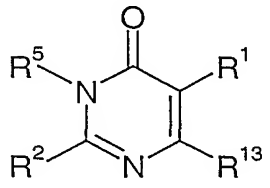
R^3 signifies hydrogen; and

Z has the significances as defined in claim 1, wherein R^9 is hydrogen.

19. A compound of formula Ie in accordance with claim 18, which is 3-(2-hydroxy-ethylamino)-5-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-[1,2,4]triazine-6-carbonitrile.

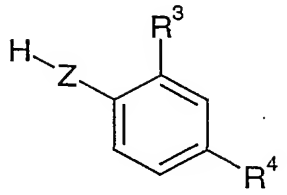
20. A process for the manufacture of compounds of formula I according to any one of claims 1 to 19 as well as of pharmaceutically acceptable salts thereof, which process comprises

a) reacting a compound of formula



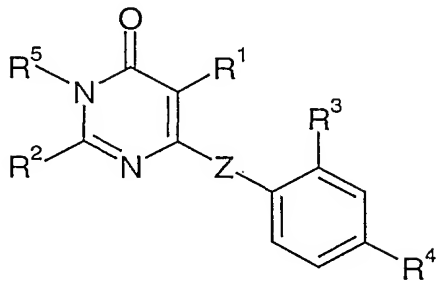
IIa

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

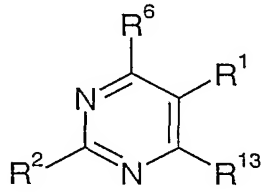


Ia

wherein R^1 to R^5 and Z have the significances as defined in claim 1,

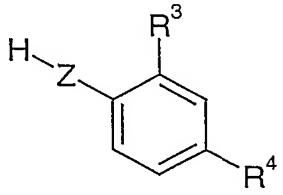
and, if desired, converting a compound of formula Ia into a pharmaceutically acceptable salt; or

b) reacting a compound of formula



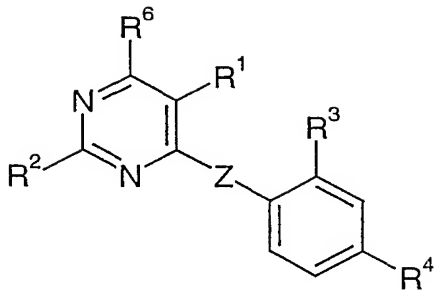
IIb

wherein R^6 and R^{13} signify halogen, with a compound of formula



III

and, if desired, substituting the halogen of R^6 with the resepctive nucleophiles to obtain a compound of formula

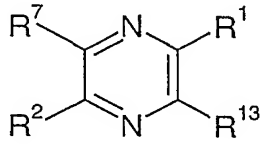


Ib

wherein R^1 to R^4, R^6 and Z have the significances as defined in claim 1,

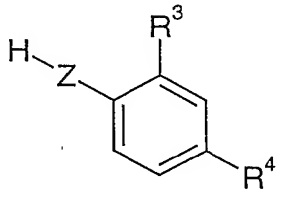
and, if desired, converting a compound of formula Ib into a pharmaceutically acceptable salt; or

c) reacting a compound of formula



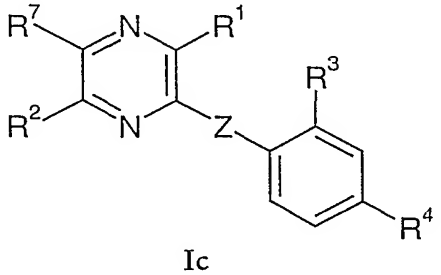
IIc

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

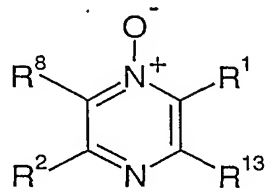


Ic

wherein R^1 to R^4, R^7 and Z have the significances as defined in claim 1,

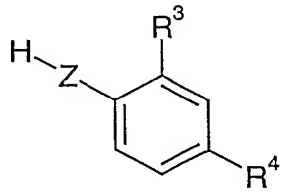
and, if desired, converting a compound of formula Ic into a pharmaceutically acceptable salt; or

d) reacting a compound of formula



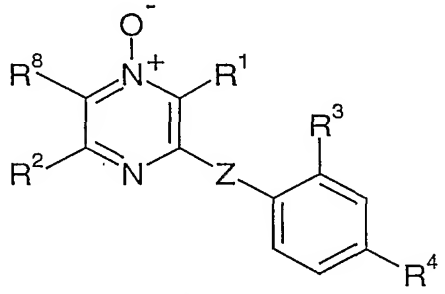
IId

wherein R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula

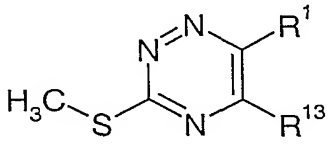


Id

wherein R^1 to R^4, R^8 and Z have the significances as defined in claim 1,

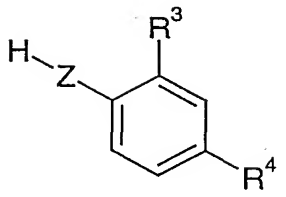
and, if desired, converting a compound of formula Id into a pharmaceutically acceptable salt; or

e) reacting a compound of formula



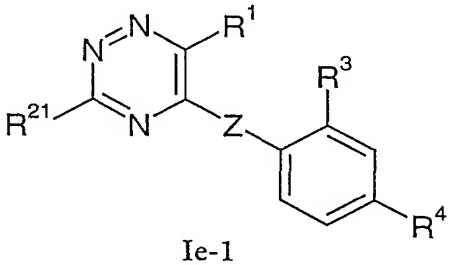
IIe

wherein R^{13} signifies halogen, with a compound of formula



III

and substituting the thiomethyl group with the respective nucleophiles to obtain a compound of formula

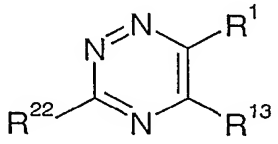


Ie-1

wherein R^{21} signifies $-NHR^{10}$ and R^1, R^3, R^4 and Z have the significances as defined in claim 1,

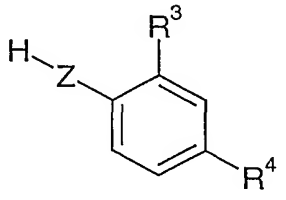
and, if desired, converting a compound of formula Ie-1 into a pharmaceutically acceptable salt; or

f) reacting a compound of formula



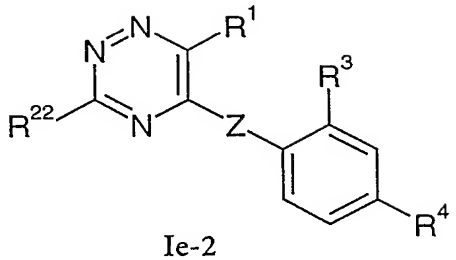
IIf

wherein R^{22} signifies $(C_1\text{-}C_7)$-alkyl and R^{13} signifies halogen, with a compound of formula



III

to obtain a compound of formula



Ie-2

wherein R^{22} signifies (C_1-C_7)-alkyl and R^1, R^3, R^4 and Z have the significances as defined in claim 1,

and, if desired, converting a compound of formula Ie into a pharmaceutically acceptable salt.

21. Compounds of formula I in accordance with claims 1 to 19, when manufactured according to a process in accordance with claim 20.

22. A medicament comprising a compound of formula I according to any one of claims 1 to 19 as well as pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients.

23. A medicament in accordance with claim 22 for the control or prevention of acute and/or chronic neurological disorders.

24. Compounds of formula I in accordance with any one of claims 1 to19 as well as their pharmaceutically acceptable salts for use in the control or prevention of diseases.

25. The use of compounds of formula I in accordance with claims 1 to 19 as well as their pharmaceutically acceptable salts for the manufacture of medicaments for the control or prevention of acute and/or chronic neurological disorders.

26. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 02/05788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D241/26 A61K31/506 C07D401/04 C07D253/06 C07D239/46
C07D239/50 C07D401/14 C07D401/12 C07D239/48 A61K31/4995
A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 074 549 A (HOFFMANN LA ROCHE) 7 February 2001 (2001-02-07) cited in the application claim 1	1,23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2002	25/10/2002

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]onal Application No
PCT/EP 02/05788

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